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Studies directed towards the stereoselective total synthesis of ilexlactone via a tandem ring-closing enyne metathesis protocol

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Abstract—Studies directed towards the stereoselective total synthesis of ilexlactone resulted in the synthesis of bicyclic systems **1a**, **1b** and *ent*-**1a** through tandem ring-closing enyne metathesis using Grubbs' catalyst. The structures of synthetic **1a**, **1b** and *ent*-**1a** revealed that the proposed structure for ilexlactone is incorrect.

The ruthenium carbenes developed by Grubbs in the early 1990s have aroused considerable attention because of their functional group tolerance and alkene chemoselection in alkene metathesis.[1] Kinoshita and Mori[2] reported ring-closing enyne metathesis with high catalytic efficiency using Grubbs' catalyst. After thorough investigations on enyne metathesis, Grubbs introduced tandem enyne metathesis in 1994.[3] In this process, various dienynes were subjected to ring-closing enyne metathesis to produce an array of bicyclic systems as well as highly complex natural products. Thus, tandem ring-closing enyne metathesis gained much prominence in synthetic organic chemistry. Recently,[4] we became interested in the synthesis of natural products as well as the synthesis of diverse compounds using Grubbs' catalyst. Consequently, we chose the natural product ilexlactone **1a**,[5] isolated from *Ilex aquifolium*, whose structure was determined as a 3-(3′-hydroxycyclopent-1-enyl)-*Z*-propenic acid-1,5′-lactone, as a synthetic target.

Though the absolute configurations at C-3 and C-5 of **1a** were not firmly established, their relative configuration was assigned as *syn*. It was thought logical to synthesize all the diastereoisomers of ilexlactone. Thus, the synthesis of **1a** was initiated with commercially available L-malic acid and 1,3-propane diol, independently, via tandem enyne metathesis as the key step. Considering previous reports[6] on tandem ring-closing enyne metathesis, it was clear that the substrates utilized so far were either electron-rich or sterically less crowded alkenes or alkynes.

Retrosynthetic analysis revealed that the target compound **1a** could be obtained from **2** by tandem ring-closing metathesis using Grubbs' catalyst (**A**) and subsequent deprotection of the MOM group. Compound **2**, in turn, could be obtained from propargyl alcohol **3** which could be prepared from L-malic acid. Retrosynthesis of the other isomer, *ent*-**1a** revealed that the key substrate **8** could be derived from chiral aldehyde **9**, which in turn could be accessed from 1,3-propane diol.

The synthesis began with known allylic alcohol **4**[7] which was subjected to Sharpless epoxidation (Scheme 1) [(−)-DIPT/Ti(O^iPr)$_4$/cumene hydroperoxide/CH_2Cl_2/−20 °C] affording an epoxy alcohol, which was chlorinated (CCl_4/Ph_3P/reflux) and then subjected to a base-induced double elimination (LDA/THF/−78 to −40 °C) to afford propargylic alcohol **3** (85%). Next, the hydroxyl group was protected as its *p*-methoxybenzyl ether (PMBBr/NaH/THF/0 °C to rt) to furnish an alkyne (86%), removal of the cyclohexanone protection (CSA/MeOH/2 h), selective silylation (TBDMSCl/imidazole/CH_2Cl_2/rt) of the primary alcohol followed by MOM protection (MOMCl/DIPEA/DMAP/CH_2Cl_2/0 °C to rt) and then removal of the silyl group

Keywords: Tandem ring-closing enyne metathesis; Sharpless asymmetric epoxidation; 1,3-Syn selective reduction; Ilexlactone.
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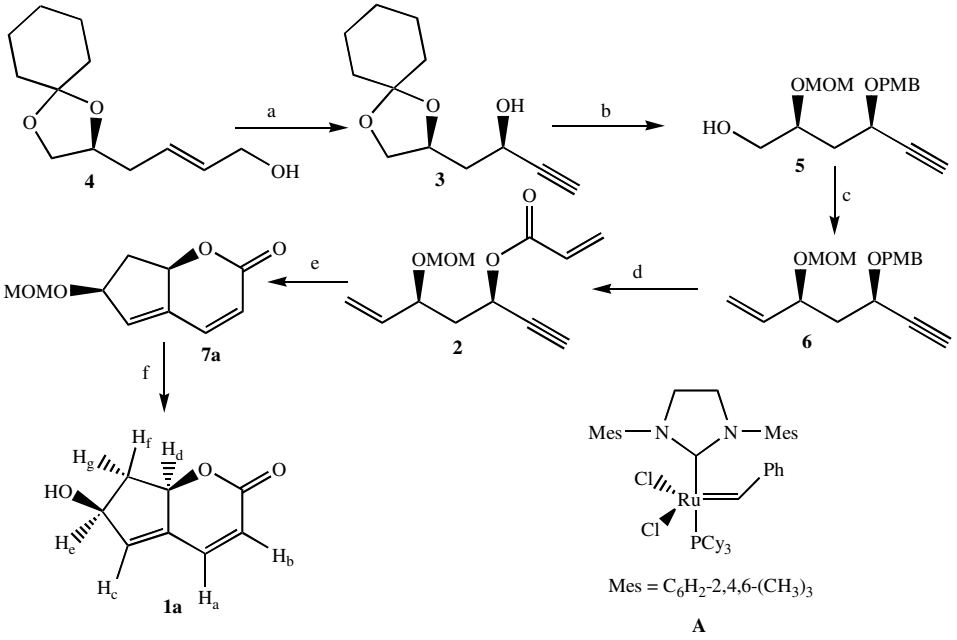
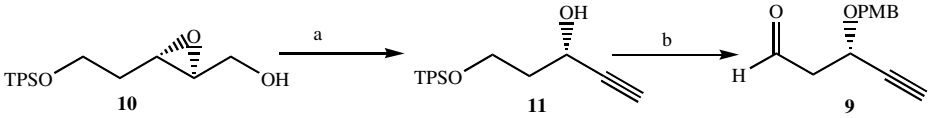


Scheme 1. Reagents and conditions: (a) (i) (−)-DIPT, $Ti(O^iPr)_4$, cumene hydroperoxide, CH_2Cl_2, −20 °C, 12 h, 85%; (ii) CCl_4, Ph_3P, $NaHCO_3$, reflux, 1 h, 90%; (iii) LDA, THF, −78 to −40 °C, 3 h, 85%; (b) (i) PMBBr, NaH, THF, 0 °C to rt, 86%; (ii) CSA, MeOH, 2 h, 81%; (iii) TBSCl, imidazole, CH_2Cl_2, rt, 84%; (iv) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C to rt, 6 h, 86%; (v) TBAF, THF, 0 °C to rt, 8 h, 90%; (c) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 91%; (ii) PPh_3CH_3I, *t*-BuOK, THF, 0 °C, 6 h, then added aldehyde, 72%; (d) (i) DDQ, CH_2Cl_2:H_2O (9:1), 0 °C to rt, 2 h, 88%; (ii) acryloyl chloride, DIPEA, CH_2Cl_2, 0 °C to rt, 1 h, 92%; (e) Grubbs' 2nd generation catalyst (**A**), 5 mol %, CH_2Cl_2, 12 h, 74%; (f) (i) PPTS, *n*-BuOH, reflux, 2 h, 83%.

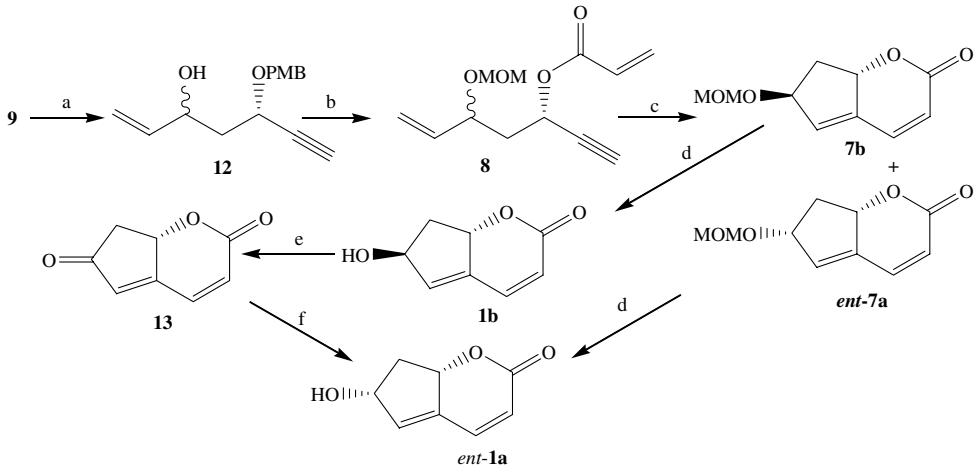
(TBAF/THF/rt) provided the desired primary alcohol **5**. Swern oxidation of **5** followed by Wittig olefination (Ph_3PCH_3I/*t*-BuOK/THF/0 °C/6 h) afforded alkene **6** (72%). Deprotection of the PMB–ether in **6** with DDQ in CH_2Cl_2–H_2O gave a propargylic alcohol which upon acryloylation (acryloyl chloride/DIPEA/CH_2Cl_2) resulted in synthon **2**. Gratifyingly, the critical tandem ring-closing enyne metathesis of **2** (**A**, 5 mol %/CH_2Cl_2/reflux/12 h) led to bicyclic system **7a** (74%). Lactone **7a** was identified from its spectral data. The ^1H NMR spectrum of **7a** indicated the absence of acetylenic and terminal olefinic protons whilst demonstrating three characteristic olefinic protons as doublets at δ 7.18 ($J = 9.5$ Hz), δ 6.04 ($J = 9.5$ Hz) and a broad singlet at δ 6.13. Further, the mass spectrum had an M+1 peak at 197 as supporting evidence. Finally, deprotection of the MOM ether (PPTS/*n*-BuOH/reflux/2 h) afforded the target molecule **1a** (83%).

The synthesis of *ent*-**1a** was initiated with known epoxy alcohol[8] **10** (Scheme 2), which was subjected to chlorination (CCl_4/Ph_3P/reflux) followed by a base-induced double elimination (LDA/THF/−78 to −40 °C) to afford propargylic alcohol **11** (85%). Next, the propargylic hydroxyl group was protected as its *p*-methoxybenzyl ether (PMBBr/NaH/THF/0 °C to rt) to afford an alkyne (86%) followed by deprotection (TBAF/THF/rt) of TBDPS to furnish a primary alcohol, which was oxidized to the corresponding aldehyde **9** under Swern conditions.

Reaction of **9** (Scheme 3) with vinylmagnesium bromide afforded an inseparable diastereomeric mixture of allylic alcohols **12** (80% combined yield in a 1:1 ratio). Compound **12** was protected as its MOM–ether (MOMCl/DIPEA/DMAP/CH_2Cl_2/0 °C to rt) followed by deprotection of the PMB–ether with DDQ in CH_2Cl_2–H_2O to afford a propargylic alcohol (86%) which upon acryloylation (acryloyl chloride/DIPEA/CH_2Cl_2) gave acrylate ester **8** (90%). Treatment of compound **8** with Grubbs' catalyst (**A**, 5 mol %/CH_2Cl_2/reflux/12 h) furnished chromatographically separable bicyclic systems *ent*-**7a** and **7b** (74%, combined yield). Deprotection of the MOM ether of *ent*-**7a** and **7b** (PPTS/*n*-BuOH/reflux/2 h) was conducted independently to afford *ent*-**1a** and its isomer **1b** (81% each). To recycle the *anti*-isomer **1b** to *ent*-**1a**, we used an oxidation–reduction protocol. Accordingly, **1b** was oxidized (Dess–Martin period-



Scheme 2. Reagents and conditions: (a) (i) CCl_4, Ph_3P, $NaHCO_3$, reflux, 1 h, 90%; (ii) LDA, THF, −78 to −40 °C, 3 h, 85%; (b) (i) PMBBr, NaH, THF, 0 °C to rt, 86%; (ii) TBAF, THF, 0 °C to rt, 8 h, 90%; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 92%.



Scheme 3. Reagents and conditions: (a) vinyl bromide, Mg, THF, then added **9**, 80%; (b) (i) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C to rt, 6 h, 84%; (ii) DDQ, CH_2Cl_2:H_2O (9:1), 0 °C to rt, 2 h, 86%; (iii) acryloyl chloride, DIPEA, CH_2Cl_2, 0 °C to rt, 1 h, 90%; (c) Grubbs' 2nd generation catalyst (**A**), 5 mol %, CH_2Cl_2, 12 h, 74%; (d) PPTS, *n*-BuOH, reflux, 2 h, 81%; (e) Dess–Martin periodinane, CH_2Cl_2, 0 °C to rt, 4 h, 85%; (f) $NaBH_4$, $CeCl_3{\cdot}7\,H_2O$, EtOH, rt, 2 h, 87%.

Table 1. Comparative ^{1}H NMR (300 MHz, $CDCl_3$) data of ilexlactone and compounds **1a**/*ent*-**1a** and **1b**

Position	Ilexlactone (reported[5])	Compound **1a**/*ent*-**1a**	Compound **1b**
	^{1}H NMR (multi, J = Hz)	^{1}H NMR (multi, J = Hz)	^{1}H NMR (multi, J = Hz)
H_a	6.65 (dd, 10.0, 2.0)	7.17 (d, 9.6)	7.19 (d, 9.63)
H_b	6.37 (dt, 10.0, 1.5)	6.02 (d, 9.6)	6.02 (d, 9.73)
H_c	5.87 (s)	6.10 (br s)	6.10 (br s)
H_d	4.93 (ddd, 12.5, 5.0, 2.0)	5.16 (t, 7.55)	5.67 (t, 6.79)
H_e	4.67(m)	4.83–4.79 (m)	5.04–5.01 (m)
H_f	2.97 (m)	3.09–2.97 (m)	2.49–2.42 (m)
H_g	1.68 (m)	2.11–1.88 (m)	2.36–2.27 (m)

inane/CH_2Cl_2/0 °C to rt) to its corresponding ketone **13** and selectively reduced[9] ($NaBH_4$/$CeCl_3{\cdot}7H_2O$/EtOH) to afford *ent*-**1a** as the exclusive product (86% over two steps). The spectroscopic data[10] (Table 1) of structures **1a** and *ent*-**1a** were found to be different from those of ilexlactone reported in the literature.[5]

Thus, it may be concluded that the structure proposed for ilexlactone is incorrect. Out of the four possible diastereoisomers, the three synthesized herein do not correspond to the proposed structure, thus discounting both the *anti*-isomers as well. Also, a comparative study of the spectral data leads to the conclusion that the most downfield proton for ilexlactone, resonating at δ 6.65, can only be rationalized if the ring system is reversed and modified into an α,β-unsaturated γ-lactone fused with a cyclohexenol thus indicating the probable structure of ilexlactone to be as shown in Figure 1. The reported ^{1}H NMR values are likely to match with this revised structure as it justifies the absence of a β-proton in the lactone ring and the presence of two olefinic protons in the cyclohexenol ring. Synthetic efforts are underway in our laboratories to make this compound.

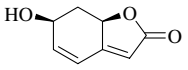


Figure 1. Probable structure of ilexlactone.

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10. *Spectral data of selected compounds*. *Compound* **2**: $[\alpha]_D^{25}$ −60.7 (*c* 0.8, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, TMS): δ 6.45 (dd, 1H, $J = 1.46$, 16.84 Hz), 6.12 (dd, 1H, $J = 10.25$, 16.85 Hz), 5.84 (dd, 1H, $J = 2.19$, 10.25 Hz), 5.76–5.5 (m, 2H), 5.30–5.19 (m, 2H), 4.65 (d, 1H, $J =$ 6.59 Hz), 4.50 (d, 1H, $J = 6.59$ Hz), 4.3–4.19 (m, 1H), 3.38 (s, 3H), 2.45 (d, 1H, $J = 2.19$ Hz), 2.21–1.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8, 137.0, 131.8, 127.8, 118.2, 93.6, 74.5, 73.9, 73.0, 61.4, 55.5, 40.2; IR (thin film) 3335, 3093, 1725 cm^{-1}; LCMS; 225 (M^++1). *Compound* **7a**: Syrup; $[\alpha]_D^{25}$ −50.9 (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, TMS): δ 7.18 (d, 1H, $J = 9.55$ Hz), 6.13 (br s, 1H), 6.04 (d, 1H, $J = 9.55$ Hz), 5.16 (t, 1H, $J = 7.53$ Hz), 4.74–4.59 (m, 3H), 3.38 (s, 3H), 3.05–2.92 (m, 1H), 2.14–1.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6, 137.0, 135.2, 134.6, 122.0, 96.3, 80.15, 79.46, 55.6, 40.3; IR (thin film) 3093, 1722 cm^{-1}; LCMS; 197 (M^++H). Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16; found: C, 61.13; H, 6.05. *Compound* **1a**: Syrup; $[\alpha]_D^{25}$ −80.6 (*c* 0.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 7.17 (d, 1H, $J = 9.63$ Hz), 6.1 (br s, 1H), 6.02 (d, 1H, $J = 9.63$ Hz), 5.16 (t, 1H, $J = 7.55$ Hz), 4.83–4.79 (m, 1H), 3.09–2.97 (m, 1H), 2.11–1.88 (m, 2H, inclusive of 1 –OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0, 137.2, 136.5, 134.9, 121.9, 80.6, 74.0, 42.3; IR (thin film): 3090, 1720 cm^{-1}; LCMS; 153 $(M+H)^+$. Anal. Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.30%; found: C, 63.05; H, 5.21. *Compound* **8**: ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 6.51–6.40 (m, 1H), 6.22–6.05 (m, 1H), 5.90–5.83 (m, 1H), 5.76–5.46 (m, 2H), 5.31–5.21 (m, 2H), 4.69–4.62 (m, 1H), 4.53–4.41 (m, 1H), 4.3–4.05 (m, 1H), 3.38 (s, 1.5 H), 3.28 (s, 1.5H), 2.46 (d, 0.5H, $J = 2.07$ Hz), 2.4 (d, 0.5H, $J = 2.07$ Hz), 2.19–1.89 (m, 2H); IR (thin film): 3340, 3093, 1722 cm^{-1}; LCMS; 225 (M^++H). *Compound* **7b**: Colored syrup; $[\alpha]_D^{25}$+47.0 (*c* 0.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 7.2 (d, 1H, $J = 9.55$ Hz), 6.16 (br s, 1H), 6.03 (d, 1H, $J = 9.70$ Hz), 5.62 (t, 1H, $J = 7.53$ Hz), 4.84–4.76 (m, 1H), 4.67–4.59 (m, 2H), 3.33 (s, 3H), 2.59– 2.44 (m, 1H), 2.34–2.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.6, 137.2, 133.0, 132.8, 122.8, 96.2, 82.4, 79.8, 55.2, 38.8; IR (thin film): 3093, 1722 cm^{-1}; LCMS: 197 (M^++H). Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16; found: C, 61.16; H, 6.10. *Compound* **1b**: Syrup; $[\alpha]_D^{25}$ −8.66 (*c* 0.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS): δ 7.19 (d, 1H, $J = 9.63$ Hz), 6.1 (br s, 1H), 6.02 (d, 1H, $J = 9.73$ Hz), 5.67 (t, 1H, $J = 6.79$ Hz), 5.04–5.01 (m, 1H), 2.49–2.42 (m, 1H), 2.36–2.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4, 137.1, 133.1, 132.7, 122.8, 82.5, 79.9, 38.9; IR (thin film): 3093, 1720 cm^{-1}; LCMS; 153 $(M+H)^+$. Anal. Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.30; found: C, 63.08; H, 5.19. *Compound ent*-**1a**: $[\alpha]_D^{25}$ +80.0 (*c* 0.05, $CHCl_3$); syrup.