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Asymmetric synthesis of (−)-*epi*-blastmycinone and (2*R*,3*S*,4*S*)-3-hydroxy-4-methyl-2-(1′-*n*-tetradecyl)-butanolide via a tungsten-mediated cyclization reaction

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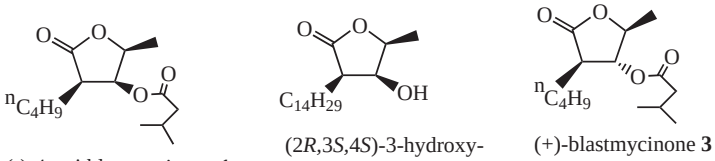
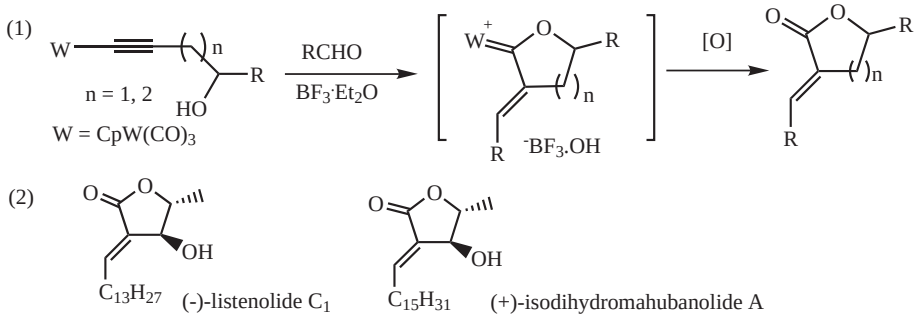
Abstract—Enantiocontrolled syntheses of the natural lactones **1** and **2** were achieved based on a tungsten-mediated cyclization. The whole syntheses comprise of six or seven steps from readily available 1-trimethylsilyl-pent-1-yne; the overall yields are 25 and 28% for **1** and **2**, respectively. © 2001 Elsevier Science Ltd. All rights reserved.

Trisubstituted natural lactones 4-*epi*-blastmycinone **1**[1,2] and (2*R*,3*S*,4*S*) - 3 - hydroxy - 4 - methyl - 2 - tetradecyl-butanolide **2** have three *cis*-substituents on a γ-lactone ring, and such sterically congested compounds are prone to elimination of the hydroxyl derivative during synthesis. Many syntheses of natural trisubstituted lactones have been directed at blastmycinone **3**,[3] and far less attention has been given to lactones **1** and **2** (Scheme 1). Compound **2** was recently isolated[4] as a trace constituent from the fruit of *Trichilia claussenii* and its biological activities remain unclear. The synthesis of its enantiomer has been reported previously.[1a]



(-)-4-*epi*-blastmycinone **1** | (2*R*,3*S*,4*S*)-3-hydroxy-4-methyl-2-tetradecyl-butanolide **2** | (+)-blastmycinone **3**

Scheme 1.



Scheme 2.

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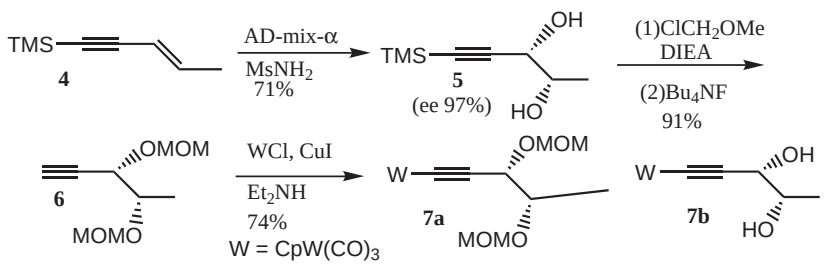
We recently reported that tungsten–alkynol complexes undergo BF_3-promoted cyclization with aldehydes to yield oxacarbeniums quantitatively (Scheme 2, Eq. (1)),[5] and give α-alkylidene-γ-lactones upon demetallation. We have utilized this cyclization for the synthesis of natural α-alkylidene-γ-lactones (−)-litsenolide C1 and isodihydromahubanolide A.[6] The synthetic sequence requires only six or seven steps from (*R*)-ethyl lactate or (*S*)-methyl lactate. In this study, we extend this cyclization to the enantioselective syntheses of trisubstituted lactones **1** and **2** in a short protocol.

Enantioselective synthesis of *syn*-diol **5** used for the cyclization is shown in Scheme 3. Asymmetric dihydroxylation[7] of enyne **4** with AD-mix-α gave (3*S*,4*S*)-1-trimethylsilyl-4-pentyne-3,4-diol (**5**) in 82% ee (93% yield), as determined by HPLC.[8] Subsequent crystallization of *syn*-diol **5** from a cold diethyl ether/hexane solution increases the ee value to 97% (71% yield). Conversion of this alcohol to its methoxymethyl ether derivative **6** was achieved in good yield according to conventional operations. Subsequent metallation of compound **6** with $CpW(CO)_3Cl$ and CuI catalyst (3 mol%) in Et_2NH[5] gave the desired alkynyltungsten complex **7a** in 74% yield. The methoxymethyl derivative **7a** is superior to its free alcohol **7b** in the cyclization reaction, and the latter forms a dioxolane species with butyraldehyde under the same conditions.

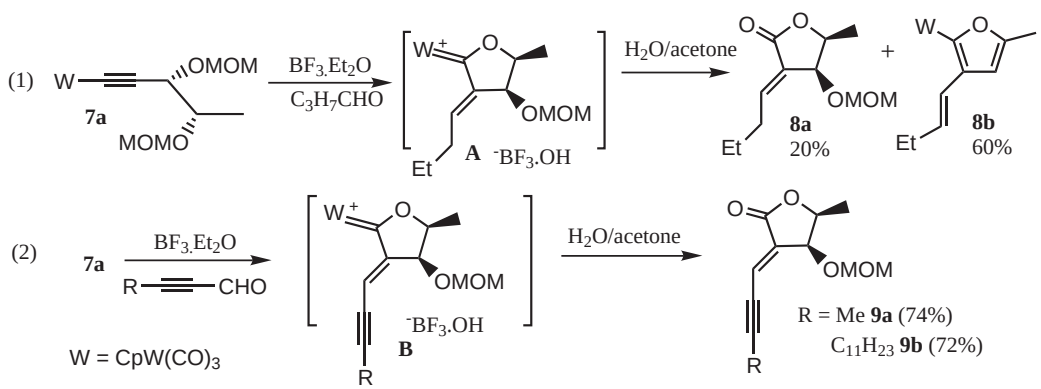
The reaction of alkynyltungsten complex **7a** with butyraldehyde and $BF_3{\cdot}Et_2O$ in cold diethyl ether (−20°C) resulted in a red precipitate, presumably the oxacarbenium salts **A** (Scheme 4). Demetallation of these salts by acetone/water in air gave the desired lactone **8a** in 20% yield; the tungsten–furyl compound **8b** was the major product (60% yield). This may suggest that the alkylidene proton of the oxacarbenium **A** is so acidic that it induces elimination of the hydroxy group. We therefore used alkynyl aldehydes RC≡CCHO (R = Me, $C_{11}H_{23}$) to avoid this elimination. Reaction with these aldehydes and $BF_3{\cdot}Et_2O$ gave oxacarbenium salts **B** in cold diethyl ether, and these salts were demetallated in acetone/H_2O to give α-alkylidene-γ-lactones **9a** and **9b** in 74 and 72% yields, respectively.

α-Alkylidene-γ-lactones **9a** and **9b** are useful intermediates for the synthesis of trisubstituted lactones. Hydrogenation of **9a** over Pd/C catalyst ($[H_2]=1.0$ atm) in CH_3OH gave lactone **10** in 95% yield (Scheme 5). Removal of the methoxymethyl group of **10** was achieved via treatment with HCl/MeOH, giving alcohol **11** in 88% yield. Further acetylation of compound **11** with isovaleryl chloride and DMAP in CH_2Cl_2 afforded *epi*-blastmycinone **1** in 86% yield. Spectroscopic data of compound **1** are consistent with those reported in the literature.[9]

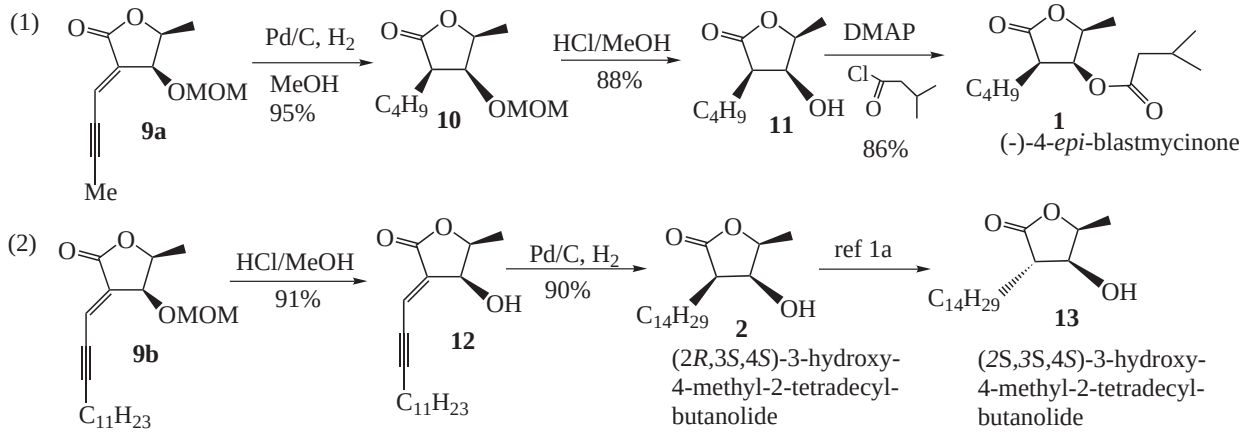
(2*R*,3*S*,4*S*)-3-Hydroxy-4-methyl-2-tetradecyl-butanolide **2** and its 2-epimer **13** were the next target molecules. The enantiomer of **13** is also a natural lactone isolated from Gorgonian coral *Plexaura Flava* in the Great Barrier Reef.[10] To target the synthesis of compound **13**, lactone **9b** was converted to alcohol **12** (91%) by removal of the MOM-protecting group upon acid hydrolysis. Hydrogenation of this alcohol over Pd/C catalyst in benzene gave the natural lactone **2**[11] rather than its epimer **13**. The hydroxy group of **12** failed to show haptophilicity and the methyl group may have prohibited the hydroxyl group from approaching the palladium surface. We also used Crabtree's catalyst[12] $[IrL(COD)Pcy_3]BF_4$ (L = pyridine) to



Scheme 3.



Scheme 4.



Scheme 5.

perform the hydrogenation in CH_2Cl_2, but this also gave lactone **2** exclusively. The epimerization of **2** to **13** can be achieved by heating **2** in benzene in the presence of DBU (41% yield) with careful control.[1a,13]

In this study, we report the enantioselective syntheses of two natural lactones **1** and **2**. The whole synthetic sequences require six or seven steps from enyne **4**, and the overall yields were 25 and 28%, respectively.

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8. The ee was determined by HPLC analysis of [(3*S*,4*S*)-3,4-di(methoxymethyl)-1-pentynyl]-benzene on a Chiral column (Merck). It was prepared by the coupling of iodobenzene with compound **6**.
9. Spectral data for compound **1**: $[\alpha]_D=-82.6$ (*c* 1.0 $CHCl_3$; lit.[1] $[\alpha]_D=-79.0$); IR (neat): 2959 (w), 2342 (s), 1780 (s), 1741 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, $J=7.6$ Hz, 3H), 0.95 (d, $J=6.4$ Hz, 6H), 1.26–1.39 (m, 7H), 1.42–1.45 (m, 1H), 1.78–1.83 (m, 1H), 2.01–2.12 (m, 1H), 2.24 (d, $J=6.8$ Hz, 2H), 2.67 (dt, $J=6.2$, 5.8 Hz, 1H), 4.55 (dq, $J=6.4$, 3.2 Hz, 1H), 5.60 (dd, $J=5.2$, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 14.0, 22.2, 22.4, 23.3, 25.5, 29.5, 42.9, 45.7, 71.9, 77.3, 172.0, 176.4; MS (75 eV, m/e): 256 (M^+). Anal. calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.61; H, 9.54.
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11. Specral data for compound **2**: $[\alpha]_D=-36.7$ (*c* 1.0, CH_2Cl_2; $[\alpha]_D=+37.2$ for its enantiomer[1a]); IR (neat): 3390 (br), 2920 (s), 1735 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, $J=6.8$ Hz, 3H), 1.18–1.44 (m, 27H), 1.59–1.65 (m, 1H), 1.72–1.80 (m, 1H), 2.24 (br, 1H), 2.53 (dt, $J=10.0$, 4.8 Hz, 1H), 4.29 (dd, $J=4.8$, 3.2 Hz, 1H), 4.43 (dq, $J=6.4$, 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 14.1, 22.6, 23.2, 27.6, 29.3, 29.4, 29.5 (two peaks), 29.6 (five peaks), 31.9, 47.6, 71.1, 178.1; MS (75 eV, *m*/*z*): 312 (M^+). Anal. calcd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found: C, 73.14; H, 11.56.
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