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PII: S0040-4039(13)01038-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.06.071
Reference: TETL 43124

To appear in: *Tetrahedron Letters*

Received Date: 9 May 2013
Revised Date: 13 June 2013
Accepted Date: 15 June 2013

Please cite this article as: Nageswara Rao, N., M. Meshram, H., Protection-free, short and stereoselective synthesis of ieodomycin A and B, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.06.071

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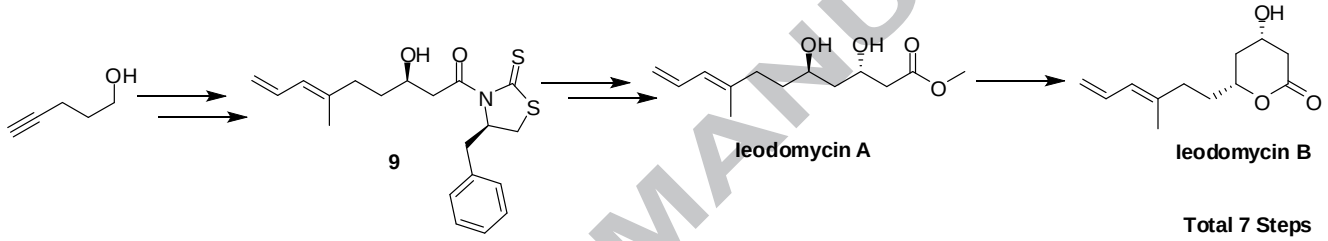

Protection-free, short and stereoselective synthesis of ieodomycin A and B

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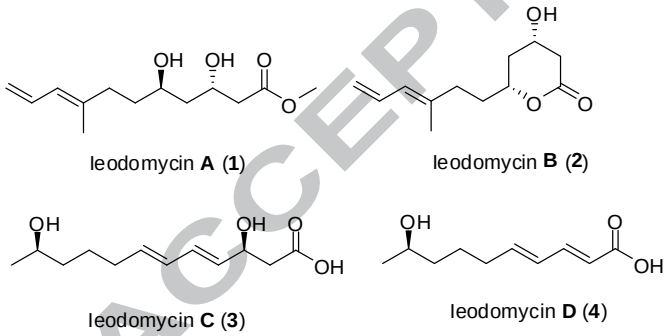
Abstract. A concise, protection-free and improved stereoselective total synthesis of ieodomycin A and ieodomycin B is described. The key steps involved in the synthesis are Evans aldol reaction and nucleophilic addition of potassium salt of mono methyl malonate.

Keywords: Evans aldol, ieodomycin, 4-pentyn-1-ol, lactonization, protection-free.

Marine life serves as a good resource of food, medicine and other raw materials that are important to mankind.[1] For decades, many biological active compounds which possess antitumor and antimicrobial activities have been discovered that are produced by a variety of marine organisms.[2] Of late, new compounds called ieodomycins **A**-**D** (Figure 1) were isolated from marine bacteria belonging to *Bacillus* species and are known to exhibit broad spectrum of antibacterial activity through inhibiting the growth of both gram positive and gram negative bacteria.[3]

Due to their promising biological activity, unique structure, and scarce availability from the natural source, the ieodomycins have attracted the attention to synthetic organic chemists. Recently, ieodomycin **C** and **D** were synthesized from propylene epoxide[4] and later ieodomycin **A** and **B** were synthesized from D-glucose based on chiral pool approach in as many as 15 steps.[5] Based on promising biological activity of ieodomycin **A** & **B**, we herein reported a short stereoselective synthesis of the ieodomycin **A** and **B**.



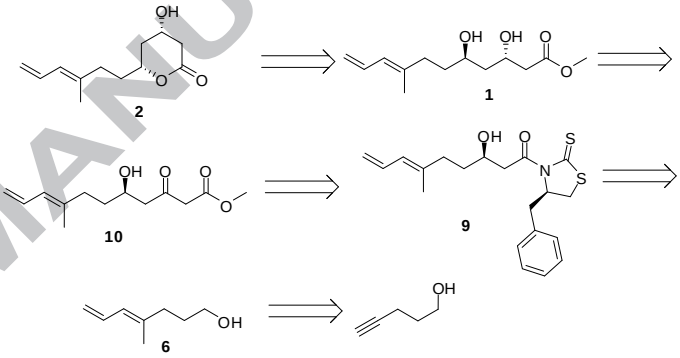
ieodomycin **A** (**1**) ieodomycin **B** (**2**)

ieodomycin **C** (**3**) ieodomycin **D** (**4**)

Figure1. Chemical structure of ieodomycin products **1-4**.

The retrosynthetic analysis of the target molecule was outlined in the Scheme 1. The synthesis of the target compound **2** was envisioned to be obtained from the anti-1,3-diol **1**, which could be derived from **10** by *anti*-hydroxy induced reduction. Compound **10** would be constructed by nucleophilic addition of aldol adduct **9** with potasium salt of mono methyl malonate. Precursor **9** was proposed to obtain from by asymmetric aldol addition of acetylthiazolidinethione onto aldehyde **7.** The compound **7** can be easily prepared by 4-pentyne-1-ol by using known literature procedures.

In a word, the proposed synthesis aims to better the existing synthesis by reducing the number of steps involved and it takes only 7 steps.

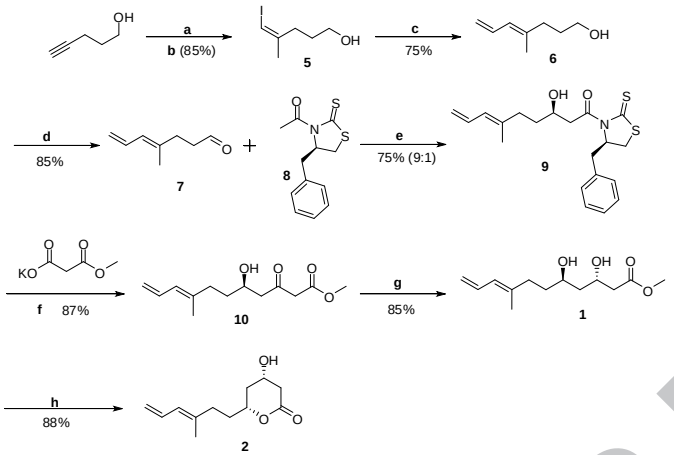


Scheme 1. Retrosynthetic analysis to **1** and **2**

The synthesis of target compounds ieodomycin **A** and **B** was illustrated in the Scheme 2. The synthesis started with 4-pentyne-1-ol converted to a methylaluminated intermediate using trimethyl aluminium and zirconcene dichloride which on treatment with iodine gave desired vinyl iodide. Coupling of vinyliodide with vinyltributyltin [6] catalyzed by palladium catalyst afforded diene **6** in 75% yield as a single isomer. The primary alcoholic functionality of compound **6** was subjected to Swern oxidation to afford the aldehyde **7**.[7] After the usual workup procedures, the aldehyde was used for the next step without further purification. Secondary alcohol **9** can be obtained by an asymmetric aldol addition of known acetylthiazolidine–thione **8** and aldyhde **7**.[8] The titanium enolate generated with titanium tetrachloride and DIPEA gave the predominantly desired isomer **9** in excellent yield.

The thiazolidinethione auxiliary of compound **9a** can be displaced by a carbon nucleophile without the need for protection of the free hydroxyl group. This protocol is adopted from an existing method.[9] Thus, treatments of aldol adduct **9** with the potassium salt of mono methyl malonate[10] and $MgCl_2$ in the presence of imidazole led to *β*-keto-ester **10**. But the reaction was too sluggish with an unacceptable yield. To enhance the rate of the reaction and yield, the reaction was performed with MgI_2. The reaction was completed within 8 h

with 87% yield. The β-hydroxy ketone was subjected to hydroxyl-directed reduction to give *anti*-1, -3-diol **1** in good yield and diastereoselectivity (85%).[11] The acid mediated lactonization of the compound afforded the target compound **2** (Scheme 2). Finally, the compound **1** was readily lactonized to compound **2** by *p*-toluene sulfonic acid or camphor sulfonic acid in benzene in 87% yield.[5] The *anti*-1, -3-diol undergoes lactonization even with silica gel to afford the target compound **2.** The optical rotation and spectral data of synthetic compounds **1** and **2** (^{1}H NMR and ^{13}C NMR) were found to be in good agreement with those of isolated natural products.[3]



Scheme 2. Synthesis of iedomycin **A** (**1**) and ieodomycin **B** (**2**). Reagents and conditions: (a) Cp_2ZrCl_2, $AlMe_3$, CH_2Cl_2 -15 ^{0}C-r.t, 12 h; (b) I_2, THF, -30 ^{0}C, K_2CO_3, 1 h; (c) Vinyl tributyltin, $Pd(PPh_3)_2Cl_2$, DMF, rt, 8 h; (d) $(COCl)_2$, DMSO, Et_3N, -78 ^{0}C, 2 h; (e) $TiCl_4$, CH_2Cl_2, DIPEA, -78 ^{0}C; 7 h; (f) MgI_2, Imidazole, THF, 5 h; (g) $Me_4NBH(OAc)_3$, AcOH/CH_3CN (1:2), -40 ^{0}C, 10 h; (h) (5 mol%) p-TsOH or CSA, C_6H_6, 0 ^{0}C.

In conclusion, we have successfully completed the stereoselective total synthesis of ieodomycin **A** and **B** from commercially available 4-pentyne-1-ol in a highly concise way and the overall yield is 26.44%. The present strategy improved an existing synthesis by achieving the target in lesser steps. A modified form of an existing methodology of chopping the auxiliary after the Evans aldol reaction was found extremely useful in this synthesis.

Acknowledgments

N N R thanks UGC for the award of a fellowship and Dr. A. Kamal, HOD, MCP Division for his support and encouragement.

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Spectral data of representative compounds:

(E)-5-iodo-4-methylpent-4-en-1-ol (**5**): IR: ν_{max} 3377, 2940, 2873, 1616, 1443, 1269, 1044, 765 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ 5.91 (s, 1H), 3.60 (t, *J* = 6.4 Hz, 2H), 2.50 (br. s, 1H), 2.29 (t, *J* = 7.6 Hz, 2H), 1.84 (s, 3H), 1.63-1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 75.0, 61.7, 35.7, 30.4, 23.8; m/z (ESI); 227 $[M+H]^+$.

(E)-4-methylhepta-4,6-dien-1-ol (**6**): IR: ν_{max} 3356, 2931, 2869, 1646, 1434, 1056, 989, 898 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$): δ 6.57 (ddd, *J* = 10.5, *J* = 10.5, *J* = 16.6 Hz, 1H), 5.88 (d, *J* = 10.5 Hz, 1H), 5.10 (d, *J* = 16.6 Hz, 1H), 5.00 (d, *J* = 10.5 Hz , 1H), 3.64 (q, *J* =12.0 Hz, 2H), 2.14 (t, *J* = 7.5 Hz, 2H), 1.77 (s, 3H), 1.62-1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.1, 125.7, 114.9, 62.5, 35.9, 30.5, 16.4; m/z (ESI); 127 $[M+H]^+$.

(R, E)-1-((R)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-6-methylnona-6,8-dien-1-one (**9**): $[\alpha]^{25}_D$ = -110 (c 1.9, $CHCl_3$); IR: ν_{max} 3447, 2925, 1696, 1341, 765 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.38 (m, 5H), 6.57 (ddd, *J* = 10.5, *J* = 10.5, *J* = 16.6 Hz, 1H), 5.91 (d, *J* = 10.5 Hz, 1H), 5.35-5.44 (m, 1H), 5.11 (d, *J* = 16.6 Hz, 1H), 5.00 (d, *J* = 10.5 Hz, 1H), 4.08-4.19 (m, 1H), 3.65 (dd, *J* = 3.0, *J* = 17.3 Hz, 1H), 3.41 (dd, *J* = 7.5, *J* = 11.3 Hz, 1H), 3.22 (dd, *J* = 3.7, *J* = 11.3 Hz, 1H), 2.99-3.18 (m, 2H), 2.89 (d, *J* = 11.3 Hz, 1H), 2.68 (br. s,

1H), 2.10-2.31 (m, 2H), 1.78 (s, 3H), 1.61-1.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.2, 172.9, 138.5, 136.2, 130.0, 129.2, 128.7, 127.1, 125.7, 114.8, 68.1, 67.2, 45.7, 36.6, 35.5, 34.1, 31.9, 16.5; m/z (ESI); 398 $[M+Na]^+$. HRMS: *m/z* calc. for $C_{20}H_{25}NO_2S_2Na$: 398.1222, found: 398.1218.

(R,E)-methyl-5-hydroxy-8-methyl-3-oxoundeca-8,10-dienoate (**10**): $[\alpha]^{25}_D$ = -33 (c 1.5, $CHCl_3$); IR: ν_{max} 3445, 2926, 1713, 1647, 1258, 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 (ddd, *J* = 10.5, *J* = 10.5, *J* = 16.7 Hz, 1H), 5.89 (d, *J* = 10.5 Hz, 1H), 5.10 (d, *J* = 16.7 Hz, 1H), 5.00(d, *J* = 10.5 Hz, 1H). 4.03-4.10 (m, 1H), 3.75 (s, 3H), 3.28 (d, *J* = 4.5 Hz, 1H), 2.81 (br, 1H), 2.73 (d, *J* = 3.2 Hz, 1H), 2.70 (d, *J* = 8.6 Hz, 1H), 2.17-2.25 (m, 1H), 2.09-2.16 (m, 1H), 1.72-1.82 (m, 1H), 1.77 (s, 3H), 1.62-1.68 (s, 1H), 1.52-1.60 (M, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.4, 167.2, 133.0, 125.8, 119.3, 115.0, 76.9, 67.0, 49.5, 41.3, 35.5, 34.3, 16.5; m/z (ESI); 263 $[M+H]^+$. HRMS: *m/z* calc. for $C_{13}H_{20}O_4Na$: 263.1252, found: 263.1253.

*(3S,5R,E)-methyl-3,5-dihydroxy-8-methylundeca-8,10-dienoate (**1**):* $[\alpha]^{25}_D$ = +17.42 (c 0.7, $CHCl_3$); IR: ν_{max} 3422, 2925, 2855, 1730, 1250, 1076 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD): δ 6.57 (ddd, *J* = 10.5, *J* = 10.5, *J* = 16.7 Hz, 1H) 5.86 (d, *J* = 10.5 Hz, 1H), 5.04 (d, *J* = 16.7 Hz, 1H), 4.93 (d, *J* = 10.5 Hz, 1H), 4.22-4.28 (m, 1H), 3.73-3.79 (m, 1H), 3.66 (s, 3H), 2.40-2.59 (m, *J* = 4.9, *J* = 9.9 Hz, 2H), 2.16-2.21 (m, 1H), 2.07-2.14 (m, 1H), 1.75 (s, 3H), 1.49-1.58 (m, 4H); ^{13}C NMR (125 MHz, CD_3OD): δ 173.9, 140.0, 134.6, 126.9, 115.0, 68.7, 66.5, 52.0, 45.2, 43.8, 37.4, 36.9, 16.7; m/z (ESI); 265 $[M+H]^+$. HRMS: *m/z* calc. for $C_{13}H_{22}O_4Na$: 265.1405, found: 265.1410.

*(4S,6R)-4-hydroxy-6-((E)-3-methylhexa-3,5-dienyl) tetrahydro-2H-pyran-2-one (**2**):* $[\alpha]^{25}_D$ = +19.63 (c 0.9, $CHCl_3$); IR: ν_{max} 3425, 2961, 2925, 1725, 1260, 1088, 1021, 799 cm-1; 1H NMR (300 MHz, CD_3OD): δ 6.58 (ddd, *J* = 10.6, *J* = 10.6, *J* = 16.6 Hz, 1H), 5.88 (d, *J* = 10.6 Hz, 1H), 5.07 (d, *J* = 16.6 Hz, 1H), 4.97 (d, *J* =10.6 Hz, 1H), 4.13-4.32 (m, 2H), 2.86 (dd, *J* = 5.3, *J* = 16.6 Hz, 1H), 2.36 (dd, *J* = 7.2, *J* = 16.8 Hz, 1H), 2.21-2.31 (m, 2H), 2.10-2.21 (m, 1H), 1.77 (s, 3H), 1.78-1.85 (m, 1H), 1.45-1.58 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 173.9, 140.0, 134.6, 126.9, 115.0, 68.7, 66.5, 52.0, 45.2, 43.8, 37.4, 36.9, 16.7; m/z (ESI); 233 $[M+H]^+$. HRMS: *m/z* calc. for $C_{15}H_{14}N_2O_2F$: 233.1145, found: 233.1144.