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# Total Synthesis of Leustroducsin B

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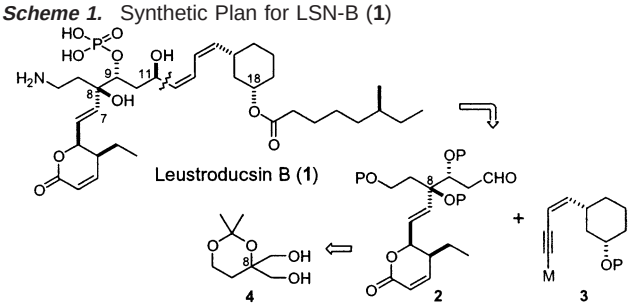
Leustroducsin B (LSN-B, **1**) is a potent colony-stimulating factor inducer isolated from the culture broth of *Streptomyces platensis* SANK 60191 by Sankyo's groups.[1,2] LSN-B is known to exhibit a variety of biological activities[3] and is likely to be developed as a new drug candidate. Recent studies suggest that LSN-B induces cytokine productions via NF-$\kappa$B activation at the transcription level as well as at the posttranscription level.[4] These interesting biological activities coupled with its unique structural features have attracted our attention as a target for total synthesis.

As illustrated in Scheme 1, we designed the construction of a carbon framework of LSN-B by coupling the aldehyde **2** and the enyne **3**. The stereochemistry of C8 of **2** was to be controlled by lipase-mediated desymmetrization of the *meso*-diol **4**.

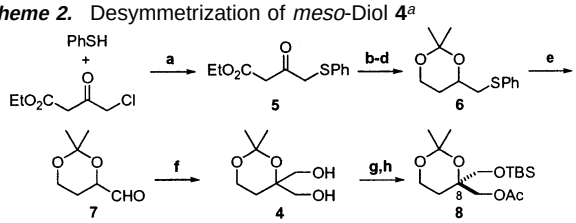
Our total synthesis commenced with the preparation of $\beta$-keto-ester **5** by treatment of ethyl 4-chloroacetoacetate with thiophenol (Scheme 2). Conversion of **5** to 1,3-dioxolane **6**, and subsequent transformations involving oxidation of the sulfide and the Pummerer reaction, afforded aldehyde **7**. Upon treatment with $(HCHO)_n$ and $K_2CO_3$, aldehyde **7** underwent aldol and Cannizzaro reactions to give *meso*-diol **4**. Desymmetrization of *meso*-diol **4** with Lipase AK in *n*-hexane-vinyl acetate furnished the optically active acetate,[5] and the remaining alcohol was immediately protected as its TBS ether **8**. This method for preparing the chiral building block **8** is operationally simple and amenable to scale-up. The enantiomeric purity of **8** was determined to be 90.2% ee by converting the acetate to the modified Mosher's ester.[6] Removal of the acetyl group of **8**, oxidation of the alcohol to the corresponding aldehyde,[7] and Wittig reaction with $Ph_3P{=}CHCO_2Et$ furnished the $\alpha,\beta$-unsaturated ester (Scheme 3). Reduction of the ethyl ester followed by deprotection of the TBS group gave a diol whose less-hindered allyl alcohol was selectively protected as the TIPS ether. The remaining alcohol was oxidized to aldehyde **9**.[7] Chelation-controlled addition of allylmagnesium bromide to the aldehyde in $Et_2O$ at $-78$ °C afforded the *sec*-alcohol **10** as a single diastereomer. Changing the protecting groups at this stage was necessary to construct the dihydropyranone moiety and to protect the diol at C8 and C9 together. The acetonide on **10** was deprotected, and the primary alcohol of the resultant triol was selectively protected to give trityl ether **11**. The remaining diol was then protected as the *p*-TBSO-benzylidene acetal **13**.[8] Because both acetonide and *p*-methoxybenzylidene acetal protecting groups for the C8,C9-diol could not be removed at the last stage of the synthesis, we devised this new benzylidene group which can be deprotected safely under weakly acidic conditions from densely functionalized substrates.

The allyl alcohol moiety of **13** was oxidized to the $\alpha,\beta$-unsaturated aldehyde **14** in a three-step sequence. The boron-mediated asymmetric aldol reaction between **14** and *n*-butyric acid derivative **15** proceeded smoothly to afford the *syn*-product **16**.[9] Protection of the secondary alcohol as the TES ether, removal of the chiral auxiliary with LiSEt, and reduction of the resultant thiolester with DIBAL[10] furnished the corresponding aldehyde, which was subsequently converted to the (*Z*)-$\alpha,\beta$-unsaturated ester

***Scheme 1.*** Synthetic Plan for LSN-B (**1**)




***Scheme 2.*** Desymmetrization of *meso*-Diol **4**[a]




[a] Reagents and conditions: (a) $Et_3N$, $CH_2Cl_2$, 0 °C; (b) $NaBH_4$, EtOH, 0 °C; (c) LAH, $Et_2O$, 0 °C; (d) $(MeO)_2CMe_2$, CSA, DMF, room temperature; (e) $O_3$, $CH_2Cl_2$, $-78$ °C; TFAA, $Et_3N$, 0 °C; (f) $(HCHO)_n$, $K_2CO_3$, MeOH, reflux (71%, six steps); (g) Lipase AK, vinyl acetate, *n*-hexane, room temperature; (h) TBSCl, imidazole, DMF, room temperature (86%, two steps).

according to Ando's method.[11] Selective deprotection of the TES group with PPTS afforded the hydroxy ester **17**, which, upon treatment with a catalytic amount of $Ti(O\textit{i}\text{-}Pr)_4$ in refluxing benzene, underwent smooth cyclization to give lactone **18**. The terminal alkene was converted into aldehyde **19** by osmium-catalyzed oxidation[12] followed by cleavage of the diol with $Pb(OAc)_4$.

The relative configuration of **18** was determined to be the desired C8−C9 anti form by the NOE studies,[13] and the absolute configuration was confirmed by the modified Mosher's method.[6]

The next step was to construct the C11 stereocenter. After extensive studies, it was found that Zn reagents proved to be very effective.[14] Thus, the alkynylzinc bromide **20**[15] underwent smooth addition to **19** in toluene−$Et_2O$ to give the desired adduct **21** as a single diastereomer. Partial reduction of the conjugated triple bond was best carried out with $Zn/LiCuBr_2$ according to the method of Brandsma[16] to yield the *Z*,*Z*-diene **22**, which was subsequently converted to phenoxyacetate **23**. It should be noted that the attempted reduction of **21** with the Lindlar catalyst as well as diimide resulted in the formation of the overreduced products.

The challenging aspect in the final stage involves a series of functional group manipulations without disturbing the other delicate functionalities. The allyl carbamate **24** was synthesized from the trityl ether **23** in a four-step sequence involving removal of the trityl group,[17] conversion of the resultant alcohol to the azide,[18] reduction of the azide by Staudinger reaction,[19] and protection of the amine with an Alloc group.[1d] Deprotection of the arylidene group required a mild two-stage procedure. Thus, the TBS group of **24** was first deprotected with $(HF)_3{\cdot}Et_3N$, and the more acid-



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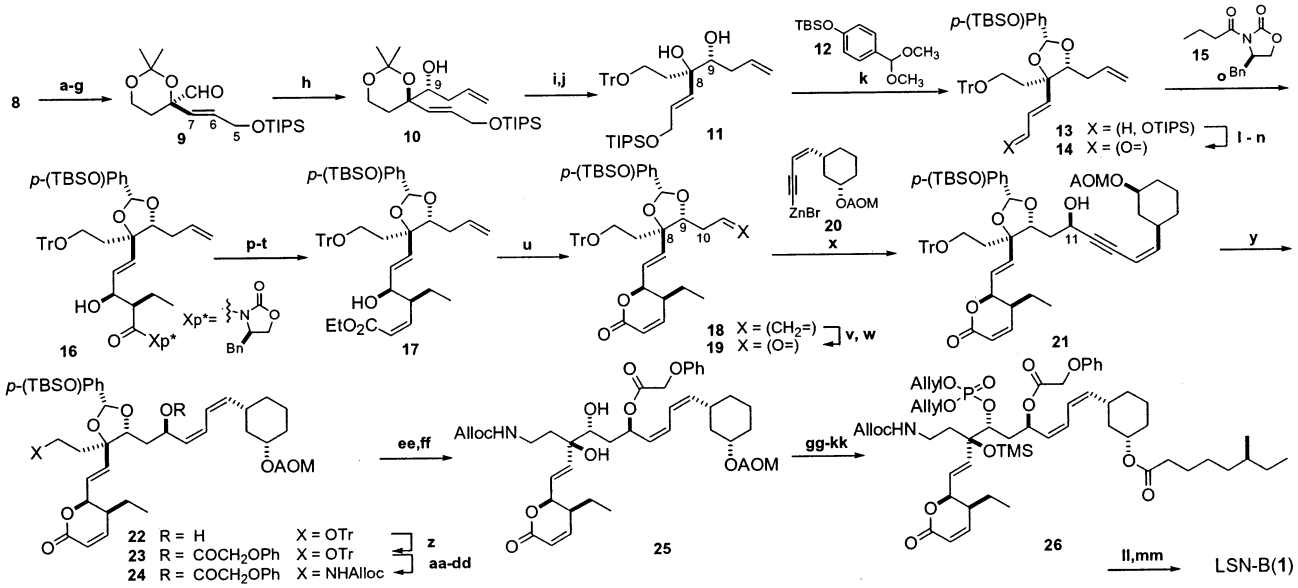
***Scheme 3.*** Total Synthesis of Leustroducsin B (**1**)[a]




[a] Reagents and conditions: (a) $K_2CO_3$, MeOH, room temperature; (b) TPAP, NMO, MS 4 Å, $CH_2Cl_2$, room temperature; (c) $Ph_3P{=}CHCO_2Et$, toluene, 100 °C (84%, three steps); (d) DIBAL, $CH_2Cl_2$, −78 °C; (e) TBAF, THF, room temperature; (f) TIPSCl, imidazole, $CH_2Cl_2$, 0 °C (83%, three steps); (g) TPAP, NMO, MS 4 Å, $CH_2Cl_2$, room temperature; (h) AllylMgBr, $Et_2O$, −78 °C (80%, two steps); (i) PPTS, MeOH, room temperature; (j) TrCl, DMAP, pyridine, 50 °C; (k) **12**, CSA, DMF, 50 °C; (l) TBAF, THF, room temperature (88%, four steps); (m) $MnO_2$, $CH_2Cl_2$, room temperature; (n) TBSCl, imidazole, $CH_2Cl_2$, room temperature (48%, two steps); (o) **15**, *n*-$Bu_2BOTf$, *i*-$Pr_2NEt$, $CH_2Cl_2$, −78 °C; (p) TESCl, imidazole, DMF, room temperature; (q) LiSEt, THF, 0 °C (72%, three steps); (r) DIBAL, toluene, −78 °C; (s) $(PhO)_2P(O)CH_2CO_2Et$, (*n*-$Bu)_4N{\cdot}OH$, THF, −78 °C; (t) PPTS, MeOH−THF, room temperature (73%, three steps); (u) Ti(O*i*-Pr)$_4$, benzene, reflux (99%); (v) $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, $NaHCO_3$, *t*-BuOH−$H_2O$, room temperature (62%); (w) $Pb(OAc)_4$, $K_2CO_3$, benzene, room temperature; (x) **20**, toluene−$Et_2O$, −78 °C to −10 °C (77%, two steps); (y) Zn, $BrCH_2CH_2Br$, $LiCuBr_2$, EtOH, reflux; (z) $PhOCH_2COCl$, pyridine, $CH_2Cl_2$, 0 °C (86%, two steps); (aa) $ZnBr_2$, $Et_3SiH$, $CH_2Cl_2$, −18 °C; (bb) PPTS, MeOH−THF, room temperature (68%, two steps); (cc) $HN_3$, $PPh_3$, DEAD, toluene, 0 °C (73%); (dd) $PPh_3$, THF−$H_2O$, room temperature; AllocCl, pyridine, room temperature (78%); (ee) $(HF)_3{\cdot}NEt_3$, THF, room temperature; (ff) AcOH−THF−$H_2O$, room temperature (57%, two steps); (gg) *N*-trimethylsilylimidazole, pyridine, room temperature; (hh) $(HF)_3{\cdot}NEt_3$, THF, room temperature (51%, two steps); (ii) $(AllylO)_2PN(i\text{-}Pr)_2$, 1*H*-tetrazole, MeCN−$CH_2Cl_2$, room temperature; *t*-BuOOH, 0 °C (79%); (jj) CAN, THF−$H_2O$, 0 °C (82%); (kk) 6-(*S*)-methyloctanoic acid, DCC, DMAP, toluene, room temperature (92%); (ll) $Er(OTf)_3$, MeOH, room temperature (68%); (mm) $Pd(PPh_3)_4$, $HCO_2H$, $Et_3N$, THF, 50 °C (51%). AOM = *p*-anisyloxymethyl.

sensitive *p*-hydroxybenzylidene group was subjected to acid hydrolysis under mild conditions to give the diol **25**. The subsequent protection−deprotection scheme furnished the free secondary alcohol at C9, which was phosphorylated to give rise to the phosphate triester.[1d,20] After removal of the AOM group with CAN,[21] the resultant alcohol was acylated with 6-(*S*)-methyloctanoic acid[1d] to yield **26**. Finally, removal of the phenoxyacetyl group on C11−OH with $Er(OTf)_3$ in MeOH followed by treatment with $Pd(PPh_3)_4$, $HCO_2H$, and $Et_3N$ furnished leustroducsin B (**1**),[1d] which was in all respects identical to natural LSN-B.[1]

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**Supporting Information Available:** Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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