CHEMOENZYMATIC FORMAL SYNTHESIS OF (-)-INDOLMYCIN[1]

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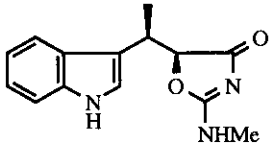
Abstract - An enantioselective formal total synthesis of indolmycin (**1**) has been accomplished based on the lipase mediated asymmetric acetylation of the prochiral diol (**5**).

Indolmycin (**1**) is an antibacterial antibiotic isolated from an African strain of *Streptomyces albus*.[2] It has been shown to be active against drug resistant *Staphylococci*,[3] *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis*.[4] This antibiotic has been known as a specific inhibitor of the tryptophanyl tRNA ligase.[5] Because of the biological profile as an antibacterial agent as well as its intriguing chemical structure, it attracted considerable interest from synthetic chemists.[4, 6] In this paper, we report a formal total synthesis of (-)-indolmycin based on the lipase catalyzed asymmetric acetylation[7] of a prochiral 2-(3-indolyl)-1,3-propanediol (**5**) in organic solvent.



indolmycin (1)

Preparation of a σ-symmetrical diol (**5**), the substrate for enzymatic reaction, was commenced with 1-benzenesulfonyl-3-iodoindole (**2**),[8] which was readily derived from indole *via* a 4-step sequence of reactions. Heck reaction[9] of **2** with the acetal (**3**)[10] provided in 82% yield of the coupled product (**4**), which was converted into the diol (**5**) in 53% yield by sequential ozonolysis and reduction with sodium borohydride ($NaBH_4$). It should be noted that the procedure is simple and efficient for the preparation of

such type of diols. With the prochiral diol in hand, we examined the optimum conditions of asymmetric acetylation using a wide variety of lipases. Of these, lipase AK catalyzed transesterification in benzene using vinyl acetate as an acetyl donor at room temperature proved to be the best of choice and the optically enriched monoacetate (**6**) was obtained in 82% yield. The enantiomeric excess of **6** was 85% as determined by ^{1}H-NMR analysis of its (*S*)-MTPA ester derivative.[11] The absolute configuration of the newly formed chiral center was deduced to be *S* in terms of the empirical rule[12] based on the chemical shift of the corresponding MTPA ester. Removal of the hydroxyl moiety in **6** by tosylation and subsequent reduction with $NaBH_4$ in DMSO[13] gave a mixture of the alcohol (**7**) and the corresponding acetate, which was immediately treated with lithium aluminum hydride to afford **7** in 83% overall yield from **6**. Sequential mesylation and cyanation gave the cyanide (**8**), which was reduced with diisobutylaluminum hydride, hydrolyzed with 10% HCl, and the resulting aldehyde was then reduced with $NaBH_4$ to give the one-carbon elongated alcohol (**9**). Treatment of **9** with *o*-nitrophenylselenylcyanide in the presence of tri-n-butylphosphine followed by oxidation with hydrogen peroxide[14] provided the terminal alkene (**10**) in 76% yield. Attempted asymmetric dihydroxylation for the construction of the another chiral center present in **1** employing AD-mix-α[15] yielded quantitatively the diol (**11**). However, it proved to be a 1:1 mixture of diastereoisomers from the ^{1}H-NMR spectrum. Therefore, we next turned our attention to the conversion of the cyanide (**8**) into the hydroxy ester (**13**), the Takeda's intermediate[6a] for (-)-indolmycin. Alkaline hydrolysis of **8** followed by treatment of the resulting acid with diazomethane produced in 83% yield of the ester (**12**), which was then exposed to the oxidation conditions of Konen and Silbert[16] to give **13**, $[\alpha]_D$+4.11° {lit.,[6a] $[\alpha]_D$+4.3°, lit.,[6b] $[\alpha]_D$+4.53°]. The IR, ^{1}H-NMR and mass spectral data of the material prepared in this way were identical with those of the authentic sample of **13**. Since the compound (**13**) has already been converted into (-)-indolmycin,[6a] the present synthesis means the formal total synthesis of it.

In summary, we have completed an alternative formal total synthesis of (-)-indolmycin employing lipase mediated asymmetric acetylation of a prochiral diol as the key step.

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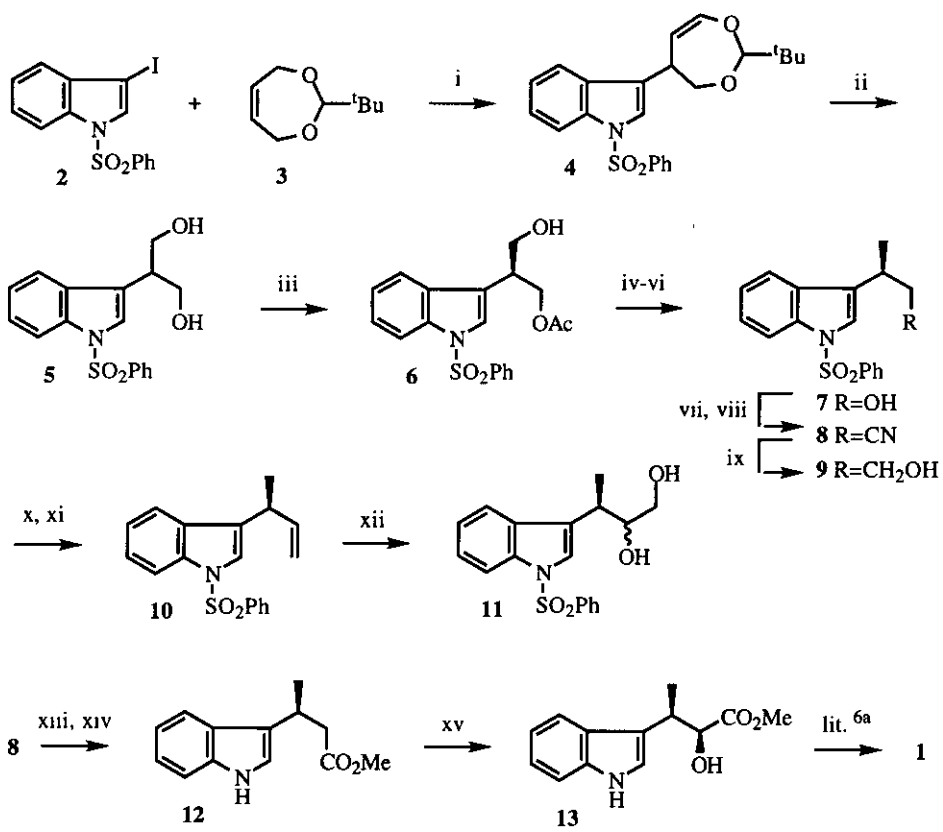

Scheme 1. ***Reagents and Conditions*****:** i, $Pd(OAc)_2$, Ph_3P, $^nBu_4NCl$, KOAc, DMF, 80 °C, 82%; ii, O_3 then $NaBH_4$, EtOH, -78°C-0 °C, 53%; iii, Lipase AK, vinyl acetate, benzene, rt, 82%; iv, TsCl, Et_3N, 4-DMAP, CH_2Cl_2, rt, 90%; v, $NaBH_4$, DMSO, 60 °C; vi, $LiAlH_4$, THF, 0 °C, 92% for the 2 steps; vii, MsCl, $^iPr_2NEt$, 4-DMAP, rt, 87%; viii, KCN, 18-Crown-6, DMSO, 60 °C, 94%; ix, DIBAH, CH_2Cl_2-hexane (1:1), -78 °C then 10% HCl; $NaBH_4$, MeOH, 0 °C, 77%; x, *o*-$NO_2PhSeCN$, $^nBu_3P$, THF, rt, 92%; xi, H_2O_2, THF, rt, 83%; xii, AD-mix-α, ^tBuOH-H_2O (1:1), 0 °C, 100%; xiii, KOH, MeOH-H_2O (3:1), reflux; xiv, CH_2N_2, Et_2O, rt, 83% for the 2 steps; xv, O_2, LDA, $(EtO)_3P$, HMPA, THF, 0 °C, 67%.

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