A Convenient Diastereoselective Synthesis of Oxazolidinone: Approach to Unusual Amino Acid Statine[1]

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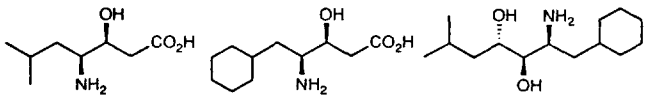
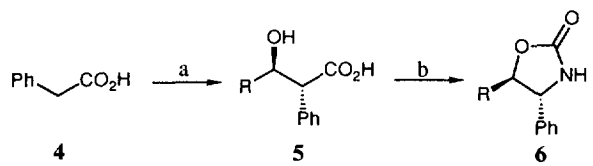
Development of new synthetic methodology for achieving stereocontrol in the construction of 1,2-aminoalcohol system has been regraded as an important objective in current organic chemistry.[3] The 1,2-aminoalcohol moieties are often found in natural products,[4] and a representative one is (3S, 4S)-4-amino-3-hydroxy-6-methylheptanoic acid known as statine (**1**) in part of didemnin.[5] Statine incorporated with appropriate peptide sequences has been known as key unit for potent human renin inhibitor[6] for an antipertensive agent. Since Danishefsky[7] reported the stereoselective synthesis of statine using a cycloaddition of a substituted diene with N-(*t*-butoxycarbonyl)leucinal, several synthetic routes[8] to statine (**1**) and related structures **2** and **3** have been explored by using natural chiral containing 1,2-aminoalcohol equivalent.



1 **2** **3**

We report herein a convenient synthetic method for oxazolidinone in a diastereoselective manner which could be valuable for the preparation of biologically active compounds possesing the 1,2-aminoalcohol moiety. The method relies on an efficient and well organized stereoselective aldol reaction[9] followed by Curtius rearrangement in order to convert carboxyl group into isocyanate to yield oxazolidinone with retention of diastereochemical relationship.[10]

Demonstration of our approach is illustrated for the synthesis of oxazolidinone **6** starting from *anti* β-hydroxy acid 5 which was prepared by the reaction of dianionic form of acid **4** with corresponding aldehyde under thermodynamic condition.[11] Reaction of β-hydroxy acid **5** with diphenylphosphoryl azide[12] in the presence of Et_3N in *t*-BuOH initially at 20℃ and then 80℃ for 6 h smoothly afforded oxazolidinone **6** in 81-87% purified yield depending on substituents. It is worth to note that none of considerable amount of minor products including possible β-eliminated acid are produced



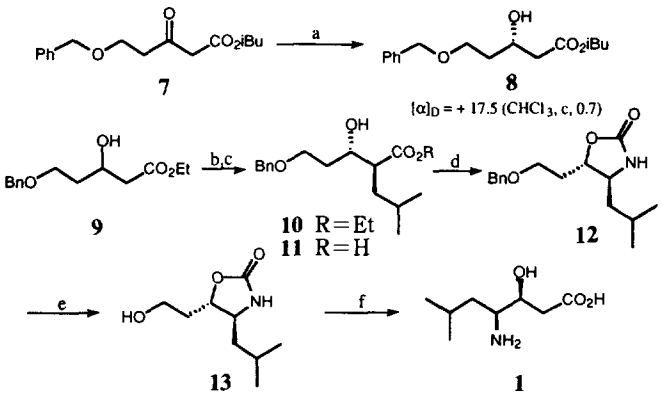
4 **5** **6**

R : a iPr b. 2-thiophene

reagents ; a. i. 2 eq. LDA, -78°C, THF ii. RCHO, -78°C-rt
b. $(PhO)_2PON_3$, Et_3N, tBuOH, rt-80°C

during the process. This result provides clear evidence for the broad generality of this method.

The scope of this approach has been enlarged by the application of its efficacy for the synthesis of statine **1**. Starting ester **8** was prepared by Baker's yeast reduction of β-ketoester 7.[13] Treatment of β-ketoester **7** with Baker's yeast at 25℃ for 3 days as described in the literature afforded β-hydroxy ester **8** in 24% yield with 94% ee.



7 **8** $[\alpha]_D = +17.5$ ($CHCl_3$, c, 0.7)

9 **10** R=Et **11** R=H **12** **13** **1**

reagents ; a. Baker's yeast, sucrose, tap water, 25°C, 3 days
b. i. 2 eq. LDA, -78°C, THF ii. iBuI, HMPA, -20°C
c. NaOH, EtOH-H_2O d. $(PhO)_2PON_3$, Et_3N, tBuOH, 80°C
e. TMSI, CH_2Cl_2 f. ref.8

With optically active **8** in our hand, we tried chelation controlled dianionic alkylation of racemic **9**. For the formation of dianion, ester **9** was added to two equivalents of LDA in THF at −78℃.[14] The resulting dianion was treated with isobutyl iodide in HMPA at −78℃ to −20℃ to yield *anti* ester **10** in 17% and diastereoselectivity turned out>20 : 1 as judged by 300 MHz ^{1}H-NMR.[15] Hydrolysis of the ester **10** to acid **11** under basic condition followed by treatment with $(PhO)_2PON_3$ gave oxazolidinone **12** in 64% isolated yield.[16] Removal of benzyl group was effected by trimethylsilyl iodide in 45% yield. Since the conversion of alcohol **13** to statine **1** is already known,[8] our method will serve as formal synthesis of statine.

In summary, this paper describes a diastereoselective synthesis of oxazolidinone in efficient and practical ways and also demonstrated its utilization for the synthesis of unusual amino acid statine in short steps.

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15. This diastereomeric purity was also confirmed by direct comparison of **11** with *anti* selective aldol products[11] (*anti* : *syn* = 3 : 1) from 4-methylvaleric acid and 3-benzyloxypropanal using ^{1}H-NMR.
16. Spectral data for **12**: mass spectrum (EI) m/z 278 (M^+, 2.3), 216 (4.2), 128 (10.9), 91 (100); ^{1}H-NMR ($CDCl_3$) δ 0.88 (d, J=6.8 Hz, 3H), 0.91 (d, J=6.8 Hz, 3H), 1.40 (m, 3H), 1.91 (m, 2H), 3.60 (dd, J=9.2, 7.5 Hz, 2H), 4.20 (m, 1H), 4.52 (s, 2H), 4.78 (m, 1H), 6.90 (br s, NH), 7.34 (m, 5H).

Studies on the Electron Transfer at Semiconductor Electrodes by Surface Modification: 1. Catalytic Activity of Iron-Substituted Heteropolytungstate Ions at Polyvinylpyridine Modified Electrode

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Electrodes coated with thin polymers and polyelectrolytes in which redox sites are incorporated have become one of the most preferred approaches for the construction of polymer modified electrode surface because of its simplicity.[1] The concept of chemically modified electrode is borne out to control the chemical nature of the electrode surface. By deliberately attaching chemical reagents or "tailor-made type" functionalities onto the electrode, the electrode would take on the chemical properties of the attached reagents. Potential applications in electrocatalytic reactions have provided much of the incentive for this development as in the case of the reduction of oxygen in Nafion coated electrode.[2] Methods for immobilizing chemical reagents on electrode surfaces are well characterized elsewhere.[3]

The most extensively used polymer films are polyelectrolyte type with electric charges on them; they are protonated or quaternized poly(4-vinyl pyridine)(L-polylysine),[1c] sulfonated or carboxylated fluoropolymers(Nafion),[4] protonated poly (4-vinyl pyridine),[5,6] random ternary copolymers,[7] poly(styrenesulfonate),[8] and cationic perfluoropolymers.[9] Requirements of such polyelectrolytes are strong, irreversible binding or adsorption to the electrode surface, reasonable ion-exchange capacities, retention of counter ionic reactants for long periods, rapid charge propagation rates within the coatings and reasonable chemical and mechanical stability. Theoretical analysis of the mechanisms and kinetics of charge propagation within polymer and polyelectrolyte coatings have been reported.[10]

Oxometalate ions which are composed entirely with inorganic elements have shown distinctive properties, especially when a transition element is substituted.[11] Electrochemical and electrocatalytic properties of iron-substituted heteropolytungstate ion in aqueous media were extensively studied by Toth and Anson.[12] Several efficient ways of immobilization or anchoring isopoly and heteropoly oxometalates on various supports have been demonstrated.[13]

This communication examines the possibility of entrapping iron-substituted heteropolytungstate ions into protonated PVP matrix and shows their electrochemical and electrocatalytic properties of the entrapped ions.

Preparation of polymer-coated electrodes was partly following the literature.[6] A stock solution of 0.5% poly(4-vinyl pyridine)(Polyscience) was prepared by dissolving PVP in 2-propanol. A solution of 0.755 mM of 1,12-dibromododecane (Aldrich) in the same solvent was prepared. Equal volumes of these two solutions were mixed and then 1-2 microliters of the mixture were applied on the polished glassy carbon