Synthetic Study on Lipid Part of Liposidomycins

Kwan Soo Kim*, Chan Seong Cheong, Jung Suk Hahn, and Jong Il Park

Department of Chemistry, Yonsei University, Seoul 120-749, Korea
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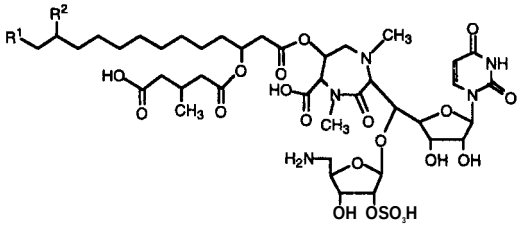
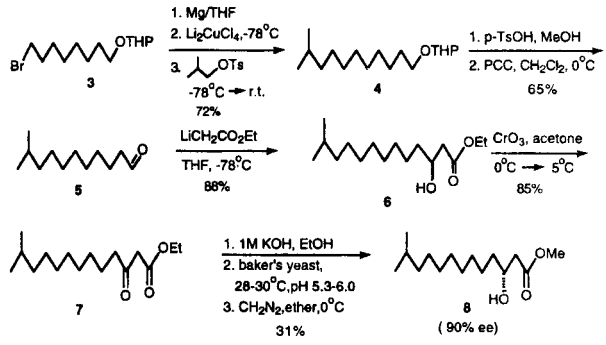
The liposidomycins are a family of novel lipid-containing nucleoside antibiotics of unusual complexity, recently found in the culture filtrate and mycelia of *Streptomyces griseosporeus,*[1] which inhibit formation of the lipid intermediate in peptidoglycan synthesis.[1,2] The primary site of action of liposidomycin C was found to be phospho-MurNAc-pentapeptide transferase, the first step of the peptidoglycan synthesis in the cell wall of *E. coli.*[3] The structures of liposidomycins B and C were proposed as **1** and **2** on the basis of degradation and spectroscopic studies.[2,4] However, six stereogenic centers in lipid and diazepanone moieties remain unassigned. We have already reported synthesis of diazepanone moiety[5] and 5-aminopentose-2-sulfate part[6,7] of liposidomycins. The present communication reports the stereoselective synthesis of one isomer among four possible stereoisomers for the lipid part of liposidomycin B.

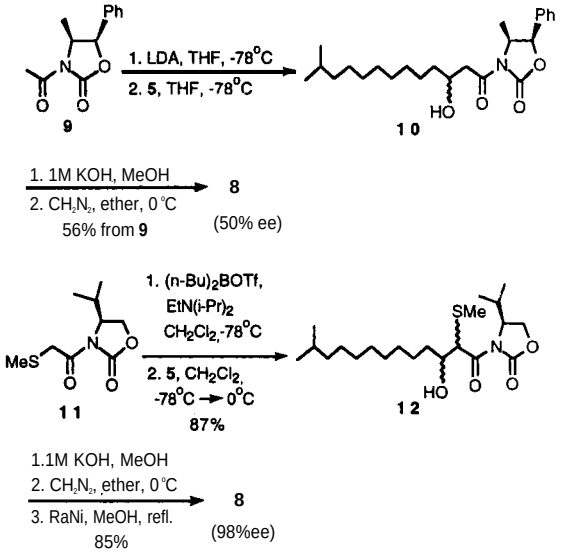


1, R^1=H, R^2=CH_3, 2, R^1=CH_3, R^2=H

The lipid part of liposidomycin B is composed of β-hydroxyisotetradecanoic acid moiety and 3-methylglutaric acid moiety. Therefore, the synthesis can be divided into three stages; stereoselective synthesis of the isotetradecanoic acid moiety, preparation of the enantiomerically pure 3-methylglutaric acid derivative, and the coupling of two moieties. Scheme 1 shows the stereoselective synthesis of β-hydroxyester **8** employing baker's yeast reduction of the corresponding β-ketoester **7.** Bromo compound **3** was prepared by the monobromination[8] of 1,8-octanediol and the subsequent protection of a remaining hydroxy group. The Grignard reagent generated from **3** was coupled with isobutyltosylate in the presence of dilithium tetrachlorocuprate[9] to afford a protected isododecanol **4**[10] in 72% yield. Deprotection of THP group in **4** with p-TsOH in methanol and oxidation of the resulting alcohol with PCC at 0 °C gave isododecanal **(5)**[11] in 65% yield. Aldol reaction of aldehyde **5** and lithium enolate of ethyl acetate afforded racemic β-hydroxyester **6.**[12] Oxidation of **6** with CrO_3 pyridine gave β-ketoester **7.**[13] Baker's yeast reduction of ester **7** proceeded only to give a hydroxyester in 5% yield probably because of low volubility of **7** in the reaction medium. Ester **7** was, therefore, hydrolyzed and the resulting ketoacid was reduced to the corresponding β-hydroxyacid with baker's yeast. The crude β-hydroxyacid was treated with diazomethane to give



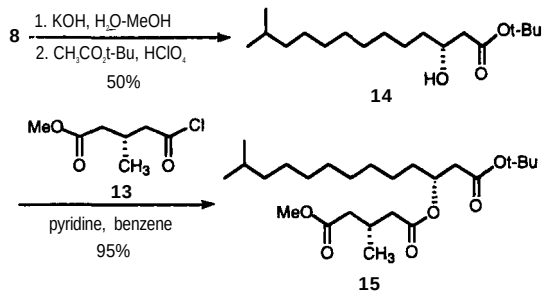
Scheme 1.



Scheme 2.

methyl (R)-(-)-3-hydroxy-12-methyltridecanoate **(8)**[14] with 90% ee in 31% yield from **7.**

Synthesis of **8** by aldol reaction of lithium enolate of chiral N-acetyloxazolidone **9**[15] and aldehyde **5** was also performed as shown in Scheme 2. The aldol adduct **10,** without isolation, was hydrolyzed and subsequently treated with diazomethane to afford **8** with 50% ee in 56% yield from **9.** Aldol reaction of boron enolate of chiral N-methylthioacetyloxazolidone **11**[15] with aldehyde **5** was found to be very stereoselective. Thus, after enolization of **11** with boron triflate and diisopropylethylamine in methylene chloride at − 78 °C for 3h, aldehyde **5** was added to the enolate and the reaction mixture was stirred for 1h at − 78 °C and 3h at 0 °C to afford **12** in 87% yield. The aldol adduct **12** was hydrolyzed with KOH, the resulting carboxylic acid was treated with diazomethane, and subsequent desulfurization with Raney nickel afforded 8 with >98% ee in 85% yield.



Scheme 3.

The optical purity of **8** was determined by Mosher's method[16] from ^{1}H NMR spectra of the (S)-MTPA esters[17] of product **8** and its racemic mixture. The absolute configuration of **8** might be predicted to be "R" by Prelog's rule,[18] by its $[\alpha]_D$ value,[19] from the earlier results of the yeast reduction of long straight-chain β-ketoacids and esters,[20] and from the earlier results of aldol reaction using the oxazolidone **9** or **11** as a chiral auxiliary.[15] The configuration of **8** was confirmed by examination of the CD spectrum of its free acid. It has been reported that the absolute configurations of α- or β-hydroxycarboxylic acids can be assigned by two characteristic bands exhibited in their CD spectra in the prescence of [Eu(fod)$_3$].[21] The CD spectrum of the free acid of **8** in the prescence of [Eu(fod)$_3$] showed a negative band in 315 nm region and a positive one in 285 nm region. The stereochemistry of compound **8** synthesized in this work is probably correct one for the eventual total synthesis of liposidomycin B. Although the configuration of the lipid part of liposidomycin B is not known at all, the stereochemistry at C-3 of the β-hydroxyacid part of liposidomycin C was inferred to be R on the basis of the $[\alpha]_D$ value of its hydrolysis product.[4]

Enantiomerically pure methyl (S)-(-)-3-methylglutarate was obtained from 3-methylglutaric anhydride by the known resolution procedure[22] and subsequently converted to the corresponding acid chloride **13** using thionyl chloride. Before coupling of compound **8** with **13,** methylester **8** was converted to *t*-butylester **14** because two ester functionalities in **15** should be distinguished for the selective removal in the later stage where the lipid part will be connected to the diazepanone part of liposidomycin B. Thus, after hydrolysis of **8,** the resulting hydroxyacid was treated with *t*-butyl acetate in the presence of a catalytic amount perchloric acid to afford **14** [23] in 50% yield as shown in Scheme 3.

Finally, reaction of **14** with **13** in benzene in the presence of pyridine gave *t*-butyl (3R,3'R)-[3-(methyl 3'-methylglutaryl)oxy]-12-methyltridecanoate **(15),** [24] the properly protected lipid part of liposidomycin B. Although it is uncertain whether compound **15** has the same stereochemistry as that of authentic liposidomycin B, the present methodology developed for the synthesis of **15** would be readily applied to the synthesis of other stereoisomers.

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10. Compound **4:** ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.85 (d, *J*= 6.0 Hz, 6H), 1.0-2.0 (m, 23H), 3.2-4.0 (m, 4H), 4,5 (brs, 1H). All new compounds gave satisfactory spectroscopic and/or microanalytical data.
11. Compound **5:** IR (neat) 1705, 2800, 2870 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, *J* =6.7 Hz, 6H), 1.10-1.70 (m, 15 H), 2.42 (m, 2H), 9.77 (t, *J* =1.7 Hz, 1H).
12. Compound **6:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, *J*= 6.7 Hz, 6H), 1.10-1.65 (m, 20H), 2.34-2.56 (m, 2H), 2.93 (brs, 1H), 3.99 (m, 1H), 4.18 (q, *J* =7.1 Hz, 2H).
13. Compound **7:** IR (neat) 1235, 1719, 1746, 2926 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, *J* =6.6 Hz, 6H), 1.12-1.80 (m, 18H), 2.54 (m, 2H), 3.43 (s, 2H), 4.22 (q, *J* =7.0 Hz, 2H).
14. Compound **8:** $[\alpha]_D^{25}$ − 11.66° (c 0.04, $CHCl_3$); IR (neat) 1470, 1748, 2859, 2936, 3464 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, *J* =6.6 Hz, 6H), 1.12-1.60 (m, 17H), 2.38-2.56 (m, 2H), 2.85 (brs, 1H), 3.72 (s, 3H), 4.01 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 25.5, 27.4, 28.0, 29.6, 29.9, 36.6, 39.1, 41.2, 51.7, 68.1, 173.5.
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17. (S)-MTPA ester of **8:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, *J* =6.6 Hz, 6H), 1.10-1.82 (m, 17H), 2.54-2.71 (m, 2H), 3.53 (s, 3H), 3.59 (s, 3H), 5.48 (m, 1H), 7.41 (m, 3H), 7.53 (m, 2H).
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19. Long straight-chain β-ketoacids and esters usually have negative $[\alpha]_D$ values in chloroform. For example, see: (a) Tulloch, A, P.; Spencer, J. F. T. *Can. J. Chem.* **1964,** *42*, 830-835. (b) Vesonder, R. F.; Wickerham, L. J.; Rohwedder, W. K. *Can. J. Chem.* **1968,** *46*, 2628-2629. (c) Nishikiori, T.; Nagasawa, H.; Muraoka, Y.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1986,** *39*, 745-754. (d)

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23. Compound **14:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, *J* =6.6 Hz, 6H), 1.12-1.80 (m, 17H), 1.48 (s, 9H), 2.28-2.48 (m, 2H), 3.09 (brs, 1H), 3.96 (m, 1H). Acetylated *t*- butylester was also obtained as a side product but readily converted to compound **14** by hydrolysis with aqueous 1 M KOH.
24. Compound **15:** $[\alpha]_D^{24}$ +1.13°(c 0.8, $CHCl_3$); IR (neat) 1157, 1368, 1746, 2853, 2922, 2971 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, *J* =6.6 Hz, 6H), 1.01 (d, *J* =6.5 Hz, 3H), 1.10-1.64 (m, 18H), 1.43 (s, 9H), 2.16-2.55 (m, 6H), 3.67 (s, 3H), 5.22 (m, 1H); MS (CI., CH_4) m/z (%) 443 (M^+, 2), 387 (100), 370 (2), 355 (9), 255 (2), 227 (7), 161 (7), 143 (27).

Observation of Both Electron and Proton Transfers in the Lowest Triplet as Well as Ground State Potential of Aqueous 6-Hydroxyquinoline

Taeg Gyum Kim, Tae Jin Yoon, and Du-Jeon Jang*

Department of Chemistry and Research Institute of Molecular Science, Seoul National University, Seoul 151-742, Korea
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The transfer reaction of charge as electron or proton is one of the most attractive fields of chemical study since it is not only omnipresent but also very important in a variety of chemical and biological processes. Photoinduced proton and electron transfer reactions in numerous molecular systems have been extensively studied recently using various time-resolved laser spectroscopic techniques.[1-7] The investigations not only provide us the vivid pictures of the reaction processes but also facilitate understanding the relations of various different properties to one another systematically. In some cases electron[8-10] and proton[1,11] transfers occur in the lowest triplet states as well. Nevertheless, very few cases have been reported in which both electron and proton transfer reactions are directly involved in the lowest triplet state potential. Even in these cases the transfers were asserted to take part in complicated photochemical processes involving exciplex formation.[12] In this brief report we show that both electron and proton reverse transfer reactions take place not only in the ground states of aqueous 6-hydroxyquinoline (6HQN) equilibrium species but also in their lowest triplet states and that the simple molecular system of 6HQN suits a good model system with which we can study consecutive proton and electron transfer reactions in a single triplet potential curve systematically.

Hydroxyquinolines and their derivatives show interesting phenomena in both fundamental and practical points of view .[13-17] The normal molecule (HQN) of aqueous 6HQN in the first excited singlet state, produced by pulse excitation, has been reported[3] to undergo protonation to the imine group first in 15 ps to transform into imine-protonated cation ($HQNH^+$), then in the time scale of 40 ps deprotonation from the enol group to turn into imine-protonated and enol-deprotonated zwitterion ($^-QNH^+$). Finally, however, quickly as in 11 ps the photochemically produced excited $^-QNH^+$ goes through intramolecular electron transfer from the deprotonated oxygen atom to the positively charged iminium ring to change into a resonance hybrid structure of quinoid-prevailing forms (Q^-NH^+) as presented in Figure 1.[3]

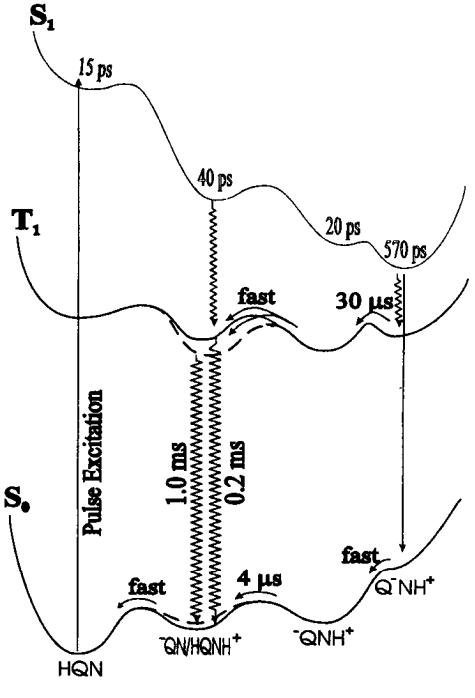

Figure 1. Schematic representation of proton and electron transfers in the first excited singlet, lowest triplet and ground states of aqueous 6HQN equilibrium species at a neutral pH. The relaxation time constants of the respective first excited singlet states are cited from the ref. 3. The relative positions of the electronic states of ^-QN, especially compared with those of $HQNH^+$ drawn with solid lines, are indicated by dotted curves.