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A FACILE METHOD FOR PREPARATION OF THE OPTICALLY PURE 3-HYDROXYTETRADECANOIC ACID BY AN APPLICATION OF ASYMMETRICALLY MODIFIED NICKEL CATALYST

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The enantioface-differentiating hydrogenation of methyl 3-oxotetradecanoate over *(R,R)*-tartaric acid-NaBr-modified nickel gave methyl *(R)*-3-hydroxytetradecanoate(III) in 85% e.e.. After III was converted to dicyclohexylammonium salt of 3-hydroxytetradecanoic acid (I), the salt was recrystallized three times from acetonitrile and was then treated with acid to give optically pure *(R)*-I in a good yield.

It has been well documented that *(R)*-*(-)*-3-hydroxytetradecanoic acid (I) is a major fatty acid composing "lipid-A" in endotoxin.[1] However, no practical way to obtain this biologically important fatty acid has been described yet. We wish to report a simple and efficient method for preparation of the optically pure-I. The present method consists of the enantioface-differentiating hydrogenation of methyl 3-oxotetradecanoate (II) over an asymmetrically modified nickel and the preferential crystallization of an optically pure substance from the hydrogenation product.

In the previous communication,[2] we reported that the modification of Raney nickel with an aqueous solution of either enantiomer of tartaric acid and NaBr gave an excellent catalyst (TA-NaBr-MRNi) for the enantioface-differentiating hydrogenation of methyl acetoacetate to methyl 3-hydroxybutyrate. The catalyst was now found to be also effective for the enantioface-differentiating hydrogenation of II to methyl 3-hydroxytetradecanoate (III). When *(R,R)*-TA-NaBr-MRNi was used as the catalyst, *(R)*-III was obtained in a large excess. The averaged enantiomer excess (e.e.) of the reaction product was found to be 85%.

The hydrogenation product was converted to a crystalline derivative of I. As far as we tested, the recrystallization of dicyclohexylammonium salt (IV) of I from acetonitrile was the most effective procedure to obtain an optically pure I. Thus, three successive recrystallization of IV of 85% e.e. gave optically pure IV in a yield of 70%.

A typical procedure for the preparation of *(R)*-I is as follows: The catalyst (*(R,R)*-TA-NaBr-MRNi) was prepared from 1.9 g of Raney nickel alloy by the same procedure as reported before.[2] The substrate II was synthesized from monomethyl malonate and dodecanoyl chloride by the published method.[3] In an autoclave (100 ml capacity), were placed II (10 g), methyl propionate (30 ml), acetic acid (0.1 ml), and *(R,R)*-TA-

NaBr-MRNi. Hydrogen was charged to a pressure of 95 kg/cm^2 and then heating was started. After the temperature of the reaction mixture had reached to 100 °C, this temperature was maintained until no more consumption of hydrogen was observed. After the evacuation of hydrogen, the raction product was dissolved in 50 ml of ether and filtered. The filtrate was washed with aqueous Na_2CO_3 solution and concentrated under reduced pressure to give 9 g of crude III. A 100 mg portion of crude III was purified on preparative TLC. Data of IR and ^{1}H-NMR of the purified sample were consistent with the structure of III. From the ^{1}H-NMR of the purified sample taken in the presence of Eu(hfmc)$_3$, the e.e. of III was determined to be 85%.

After the saponification of crude III (8.4 g) by conventional method, the resulting crude acid was treated with 6.3 g of dicyclohexylamine dissolved in 50 ml of ethanol at room temperature.

The evaporation of ethanol from the mixture gave 13.0 g of crude IV as crystals. Three successive recrystallizations from acetonitrile gave 10.1 g of chemically and optically pure IV,[4] mp 94-5 °C, Found: C, 73.37 %; H, 12.28 %: N, 3.19 %; Calcd. for $C_{26}H_{51}NO_3$:C, 73.36 % H, 12.08 %; N, 3.29 %, $[\alpha]_D^{20}$-4.4° (*c* 2.0, methanol).

From optically pure IV, *(R)*-I was obtained almost quantitatively, mp 73 °C, $[\alpha]_D^{20}$ -16.2° (*c* 1.0, $CHCl_3$) lit.[5] $[\alpha]_D^{25}$-16° (*c* 2, $CHCl_3$). The overall yield of *(R)*-I from II was calculated to be 61.3 %.

(S)-I, $[\alpha]_D^{20}$+16.0° (*c* 1.0, $CHCl_3$) was also obtained in a yield of 64.5 % from the hydrogenation product with *(S,S)*-TA-NaBr-MRNi by the same procedure as mentioned above.

References and Notes

1) C. Galanos, O. Lüderitz, E. T. Rietschel, and O. Westphal, Internat. Rev. Biochemistry, Biochemistry of Lipids II, Vol. 14, p. 239, University Park Press, Baltimore, 1977.
2) T. Harada and Y. Izumi, Chem. Lett., 1978, 1195.
3) W. Wierenga and H. I. Skulnick, J. Org. Chem., 44, 310 (1979).
4) At this stage of the recrystallization, the optical rotation of IV reached constant value unchanged by further recrystallization. The optical purity of III derived from IV was also checked by NMR with Eu(hfmc)$_3$.
5) M. Ikawa, J. B. Koepfli, S. G. Mudd, and C. Niemann, J. Amer. Chem. Soc., 75, 1035 (1953).

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