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Studies towards lipid A: a synthetic strategy for the enantioselective preparation of 3-hydroxy fatty acids

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Abstract—A short and efficient enantioselective synthesis of (*R*)-3-hydroxydodecanoic acid is described, involving a Sharpless asymmetric dihydroxylation to produce the required (*R*)-stereochemistry.

1. Introduction

Greater interest has been taken in 3-hydroxy fatty acids by both synthetic chemists and glycobiochemists.[1] In particular, the fatty acid chain length appears to be a significant determinant of bioactivity in lipid A molecules, whose (*R*)-3-hydroxytetradecanoic acid is the most common fatty acid constituent. Recently published results have established[2] the unusual structure of the lipid A family (Fig. 1) derived from LPS of *Halomonas magadiensis*, a bacterium which is non-pathogenic in humans. This lipid A has been shown to consist of a complex and heterogeneous mixture of disaccharides variously acylated with primary (*R*)-3-hydroxydodecanoic acid.

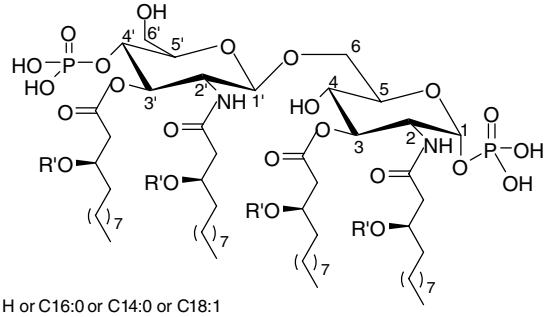

Figure 1.

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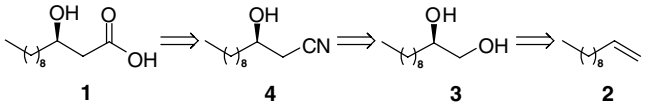


Scheme 1. Retrosynthetic path.

Since lipid A from *H. magadiensis* interferes with cytokine induction in human cells,[3] it would be very interesting to observe the biological activity of each component of this lipid A as a potential antagonist. We are currently developing a flexible procedure for the facile synthesis of its constituents and, within this context, an efficient preparation of lipidic moieties with high enantiomeric excess is also required. Herein, we report a new approach to the enantioselective synthesis of (*R*)-3-hydroxydodecanoic acid **1** in high yield and enantiomeric excess.

While many syntheses of (*R*)-3-hydroxytetradecanoic acid derivatives have been achieved by both chemical and enzymatic methods,[4] few procedures[5] are reported for a large scale preparation of (*R*)-3-hydroxydodecanoic acid **1**. We planned to start from the commercially available 1-undecene **2** as outlined in the retrosynthetic path in Scheme 1.

2. Results and discussion

Our strategy involved homologation of the 1-undecene carbon chain through the displacement of the primary hydroxyl of chiral diol **3** with a cyano group. The chiral diol **3** was prepared in high yield (82%) by the Sharpless asymmetric dihydroxylation reaction[6] on alkene **2** using AD-mix-β. This reagent produced the asymmetric carbon atom

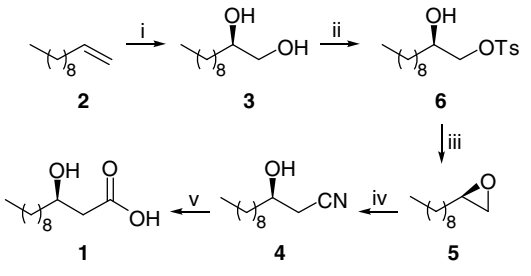
with the required (*R*)-stereochemistry. The enantiomeric excess (90%) was determined by ^{1}H NMR spectroscopy of the corresponding 1-methoxy derivative using the chiral shift reagent Eu(hfc)$_3$ in comparison with a racemic mixture.[7]

Concerning the conversion of diol (*R*)-(−)-**3** into the cyanoalcohol (*R*)-(−)-**4**, we believed that it could be available through the regioselective opening of the chiral epoxide **5** that can be produced, as reported,[8] by using a betaine-like intermediate. In fact, activated phosphorus reagents such as DTPP, TPP–CCl_4–K_2CO_3 and TPP–DEAD promote cyclodehydration of unsymmetrical chiral diols to afford epoxides with retention of stereochemistry at the chiral carbon. Drawing on our previous[9] experience with a polystyryl diphenyl phosphine/iodine (PDP/I_2) complex, we chose to achieve the required chiral epoxide **5** using TPP/I_2 in the presence of potassium carbonate in anhydrous acetonitrile. However, under our conditions, the yield of **5** was less than 50%. When the reported[8] reagent TPP–CCl_4–K_2CO_3 was employed, similar results were obtained. These findings prompted us to follow an alternative synthetic procedure for the preparation of **5** (Scheme 2).

Firstly the primary alcohol was regioselectively converted[10] in high yield (95%) into the monotosyl[11] compound **6** by treatment with dibutyltin oxide (0.02 equiv), followed by the addition of *p*-toluenesulfonyl chloride (1.0 equiv) and triethylamine (1.1 equiv) in anhydrous dichloromethane. The treatment[12] of (*R*)-(−)-**6** in basic methanolic solution afforded[13] (*R*)-(+)-1,2-epoxyundecane **5** in 91% yield, with complete retention of the C-2 configuration.

The regioselective ring opening using TBAF/TMSCN in anhydrous tetrahydrofuran at room temperature gave cyanoalcohol (*R*)-(−)-**4** in 89% yield.[14] Finally, the synthesis was completed successfully by hydrolysis of intermediate **4**, which was carried out[15] through the action of alkaline hydrogen peroxide in aqueous methanol to obtain (*R*)-3-hydroxy acid **1** in 81% yield with an enantiomeric excess of 88%.

Since the synthesis of the components of lipid A needed (*R*)-3-hydroxydodecanoic acid **1** with a high enantiomeric excess, we purified crude **1** thus obtained, using Tai's method,[5a] which involves its conversion into the corresponding *N*,*N*-dicyclohexylammonium salt. The enantiomerically pure[16] acid **1** (ee >99%) was obtained in 76% yield by three successive recrystallizations from acetonitrile and acid treatment of the salt.



Scheme 2. Reagents and conditions: (i) AD-mix-β, methanesulfonamide, *t*-BuOH/H_2O, rt, 16 h, 82%; (ii) dibutyltin oxide, *p*-TsCl, NEt_3, CH_2Cl_2 anhydrous, rt, 50 min, 95%; (iii) NaOH, MeOH, 0 °C, 30 min, 91%; (iv) Me_3SiCN, TBAF, THF, 50 °C, 16 h, 89%; (v) a. NaOH/H_2O_2, MeOH, reflux, overnight, 81%; b. 2 M aq HCl, rt; c. (*c*-$C_6H_{11})_2NH$, MeCN, MeOH, reflux, 30 min; d. 10% aq HCl, 0 °C, 10 min, 76%.

3. Conclusion

Herein, we reported a practical, highly enantioselective synthesis of (*R*)-3-hydroxydodecanoic acid **1** with high overall yield (39%) from a commercial starting product, using a Sharpless AD reaction as source of chirality. The synthetic strategy described here can be extended to other β-hydroxy fatty acids and related analogues.

Acknowledgements

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6. AD-mix-β (26.4 g) and $MeSO_2NH_2$ (1.8 g, 19.4 mmol) were added to a stirring solution of **2** (3.0 g, 19.4 mmol) in ^{t}BuOH/H_2O (220 mL, 1:1) at room temperature. After the starting product was completely consumed (TLC, 16 h), the mixture was quenched by the addition of 0.4 equiv of Na_2SO_3, stirred for 1 h and then concentrated under reduced pressure. Silica gel column chromatography of crude product using $CHCl_3$ as eluent led to diol **3** as a white crystalline solid, after recrystallization from hexane/acetone 9:1 (3.0 g, 82% yield). Mp 50.0–51.0; $[\alpha]_D^{25} = -6.2$ (*c* 2.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, $J = 6.8$ Hz, 3H), 1.23–1.29 (m, 14H), 1.41–1.53 (m, 2H), 1.77–2.12 (m, 2H), 3.45 (dd, $J = 7.6$, 10.9 Hz, 1H), 3.68 (dd, $J = 2.9$, 10.9 Hz, 1H), 3.71–3.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 23.0, 25.9, 29.7, 29.9 (2 × C), 30.0, 32.2, 33.6, 67.2, 72.7. Anal. Calcd for $C_{11}H_{24}O_2$: C, 70.16; H, 12.85. Found: C, 70.37; H, 12.89.
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11. Monotosylate **6**: oil $[\alpha]_D^{25} = -9.2$ (*c* 2.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.0$ Hz, 3H), 1.10–1.34 (m, 14H), 1.35–1.50 (m, 2H), 2.46 (s, 3H), 3.80–3.86 (m, 1H), 3.88 (dd, $J = 7.3$, 9.8 Hz, 1H), 4.04 (dd, $J = 2.4$, 9.8 Hz, 1H), 7.36 (d, $J = 8.0$, 2H), 7.81 (d, $J = 8.0$, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 22.8, 25.4, 29.5, 29.7, 29.9, 32.1, 32.9, 69.7, 74.2, 128.2, 130.2, 133.8, 145.3. Anal. Calcd for $C_{18}H_{30}O_4S$: C, 63.13; H, 8.83; S, 9.36. Found: C, 63.38; H, 8.80; S, 9.40.
12. Our attempts to obtain cyanoalcohol (*R*)-(−)-**4** by the direct nucleophilic displacement of tosylate **6** with tetraethylammonium cyanide were unsuccessful.
13. $[\alpha]_D^{25} = -9.7$ (neat). The spectroscopic data were in full agreement with the values of the racemic mixture reported in the literature: Sato, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Panyella, D.; Notori, R. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 905–915.
14. A stirring solution of compound **5** (2.3 g, 13.7 mmol) in anhydrous THF (68 mL) was treated with Me_3SiCN (2.0 g, 20.5 mmol) and 1 M solution of TBAF in the same solvent (5.9 mL) at 50 °C. After 16 h (TLC; $CHCl_3/CH_3OH = 95:5$) the reaction was concentrated and the mixture, diluted with water (10 mL), was extracted with AcOEt (2×50 mL). The organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Silica gel column chromatography of crude product (1:20, Etp/$Et_2O = 95:5$) afforded the oily compound **4** (2.3 g, 89% yield). $[\alpha]_D^{25} = -4.3$, (*c* 3.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.8$ Hz, 3H), 1.20–1.38 (m, 14H), 1.52–1.68 (m, 2H), 2.48 (dd, $J = 6.3$, 16.6 Hz, 1H), 2.57 (dd, $J = 4.8$, 16.6 Hz, 1H), 3.80–4.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.5, 25.3, 25.9, 26.0, 28.5, 29.2, 29.3, 31.7, 36.5, 67.7, 117.6. Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.79; H, 11.71; N, 7.13.
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16. Pure (*R*)-(−)-3-hydroxydodecanoic acid **1**: white crystals. Mp 57.5–58.0 °C; $[\alpha]_D^{25} = -17.8$ (*c* 1.2, $CHCl_3$) [lit.[5a] $[\alpha]_D^{20} = -17.5$ (*c* 1, $CHCl_3$)]; ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.8$ Hz, 3H), 1.22–1.59 (m, 16H), 2.47 (dd, $J = 9.3$, 16.0 Hz, 1H), 2.57 (dd, $J = 2.9$, 16.6 Hz, 1H), 4.00–4.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 22.6, 25.3, 29.2, 29.4, 31.7, 36.4, 41.0, 67.9, 177.5. Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.48; H, 11.20.