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A practical preparation of enantiomerically pure (*R*)- and (*S*)-2-bromohexadecanoic acids

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Abstract

The efficient preparation of enantiomerically pure (*R*)- and (*S*)-2-bromohexadecanoic acids with e.e.>95% through resolution with the use of a recoverable chiral auxiliary is described. The procedure involves three reactions: Steglich esterification, DIBAL reduction, and Sharpless oxidation. The assessment of the enantiomeric purity is based on NMR analysis by using (1*R*,2*R*)-(+)-diphenylethane-1,2-diamine as a chiral solvating agent.

1. Introduction

Determination of the absolute configuration of chiral molecules holds great scientific and technical importance, and has been a very active research subject. X-ray diffraction, polarimetry, NMR analysis, and circular dichroism are among the established and commonly used methods. In 1998, Flynn and coworkers reported the direct determination of the chirality of organic molecules by scanning tunneling microscopy (STM).[1] When (*RS*)-2-bromohexadecanoic acid was adsorbed as a two-dimensional crystal onto the basal plane of graphite, these molecules segregated on the surface into domains of pure (*R*) or (*S*) enantiomers. The atomic resolution obtained in the STM images of these species allows a direct assignment of the chirality of individual molecules. When assigning the identity of atoms in the images of 2-bromohexadecanoic acid, it was assumed that the molecules were lying *trans* in the plane. The dark spot was assigned to the carboxyl group and the large bright spot was assigned to the bromine atom, which is thought to necessarily point up from the graphite substrate. All of these assumptions are well supported by previous studies.[2] However, it is necessary to obtain an enantiomerically pure sample, image it, and compare the domains to the previously imaged domains. To this end, enantiomerically pure (*R*)- and (*S*)-2-bromohexadecanoic acids have to be made available. The desired enantiomeric excess (e.e.) was set to be >95%.

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There are two conceivable methods to prepare enantiomerically pure (*R*)- and (*S*)-2-bromohexadecanoic acids with e.e. higher than 95%: a multi-step synthesis or resolution of the racemic 2-bromohexadecanoic acid, which is commercially available and inexpensive. Basically, two synthetic protocols have been reported in the literature: (1) diastereoselective bromination,[3] and (2) enantioselective diazotization and bromide displacement processes.[4–6] As far as the title compounds are concerned, diastereoselective bromination followed by removal of the chiral auxiliary allowed synthesis of both enantiomers of 2-bromohexadecanoic acid with an e.e. of about 70%.[7] Alternatively, the racemic α-haloalkanoic acids can be separated by chemical or biochemical resolution. In the literature, an attempt to prepare (+)-2-bromohexadecanoic acid by lipase-catalyzed enzymatic resolution of (±)-2-bromohexadecanoic acids was reported.[8] Unfortunately, no information about its absolute configuration or its e.e. was given. To the best of our knowledge, to date no well-established procedure is available to prepare both (*R*)- and (*S*)-2-bromohexadecanoic acids with e.e. higher than 95%.

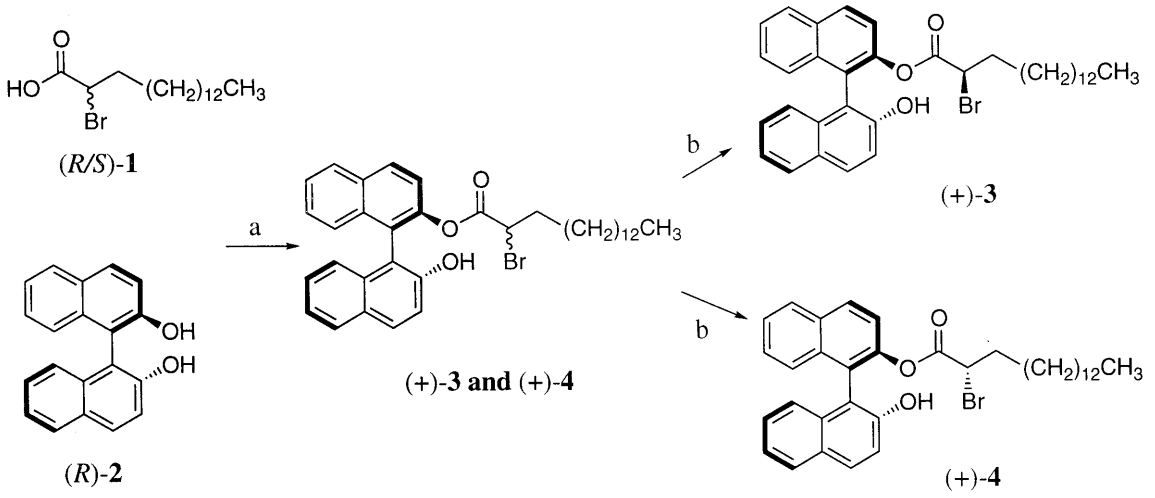
2. Results and discussion

There are two main difficulties in obtaining enantiomerically pure (*R*)- and (*S*)-2-bromohexadecanoic acids with high e.e. First, the stereogenic center in the molecule is unstable under both acidic and basic conditions. The isomerization of the stereogenic center may occur through enolate formation. Second, the long carbon chain makes 2-bromohexadecanoic acid different from 2-haloalkanoic acids with short chains, which are the common substrates studied in the references. Many methods provide excellent results on short-chain compounds, but fail on the 16-carbon compounds. For example, the kinetic resolution by lipase worked very well with 3-carbon compounds, affording products with e.e. 95% or higher.[8] However, the e.e. of the 6-carbon product was about 73%.[8] When we applied this method to 2-bromohexadecanoic acid, the e.e. of the resolved acid was about 60% or lower. Dehydroabiethylamine was used as a resolving agent to resolve racemic 2-bromobutyric acid by forming two diastereomeric salts, one of which crystallized while the other was left in the solution.[9] When dehydroabiethylamine was combined with racemic 2-bromohexadecanoic acid, the reaction mixture underwent a rapid precipitation instead of the desired fractional crystallization. This drastic difference between our experiment and the result with 2-bromobutyric acid was assumed to come from the difference in the chain length.

From the very beginning, we intended to avoid multi-step syntheses, and planned to make the products in an efficient manner. After we tested the resolution with lipase and dehydroabiethylamine and no satisfactory results were obtained, we decided to focus our effort on resolution with chiral alcohols, which ended up with success.

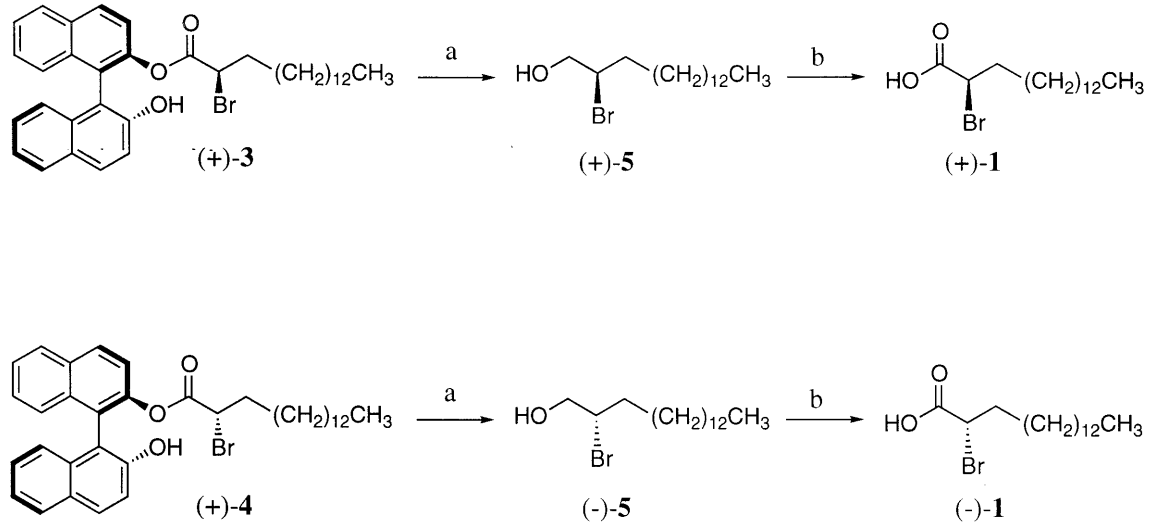
The idea of using a chiral alcohol to resolve racemic acids is straightforward. Theoretically, two reactions and one separation would be necessary. First, the racemic acid is reacted with the chiral alcohol to give two diastereomeric esters. These two diastereomers should be separable on thin layer chromatography (TLC) and by column chromatography. After the separation, the chiral auxiliary is removed without isomerizing the stereogenic centers, to yield the enantiomerically pure acids. Hydrolysis under acidic or basic conditions is the common method for such removal. However, since the stereogenic center in 2-bromohexadecanoic acid is sensitive to both acidic and basic conditions, the hydrolysis conditions must be as mild as possible, or a two-step procedure, reduction and re-oxidation, should be explored. With this idea in mind, we screened

several 'chiral alcohols' for the esterification. These 'chiral alcohols' included (1*R*,2*S*,5*R*)-(−)-menthol, (*R*)-(+)-*sec*-phenethyl alcohol, (1*S*)-*endo*-(−)-borneol and (*R*)-(+)-1,1′-bi-2-naphthol. Experimental results demonstrated that (*R*)-(+)-1,1′-bi-2-naphthol afforded the best separation. The diastereomers from the esterification reaction of (*R*)-(+)-1,1′-bi-2-naphthol with racemic 2-bromohexadecanoic acid showed two spots on TLC and could be separated in large quantity by column chromatography (see Scheme 1). The rationale behind selecting (*R*)-(+)-1,1′-bi-2-naphthol as the 'chiral alcohol' was that a phenol ester was supposed to be easier to hydrolyze than alcohol esters, so hydrolysis conditions to remove the chiral auxiliary might be tuned mild enough to avoid epimerization of the chiral center.



Scheme 1. (a) DCC, DMAP, CH_2Cl_2, rt. (b) Separation via MPLC (see Section 4)

The experimental procedure is shown in Schemes 1 and 2. The first step was a Steglich esterification reaction. The total yield of two diastereomeric mono-esters, **3** and **4**, was 92%.



Scheme 2. (a) DIBAL, −78°C, CH_2Cl_2. (b) $NaIO_4$, $RuCl_3$, $CCl_4/CH_3CN/H_2O$, rt

Bis-ester was isolated in 8% yield and characterized by NMR and MS measurements. After two times of development in 10:1 hexanes:EtOAc, the solution of the mono-esters clearly showed two distinct spots on the TLC silica gel plate, both under UV detection at short wavelength and after staining with CAM (cerium(IV) sulfate and ammonium molybdate in 10% aqueous H_2SO_4) solution. The R_f values of these two spots were 0.5 and 0.4, respectively. The almost equal intensity on TLC plate and the roughly 1:1 ratio of peak integration in the NMR spectrum of the mixture suggested that there was no kinetic resolution. In other words, the two acid enantiomers reacted with the chiral auxiliary at almost the same rate.

Although the two diastereomers were separable by plate chromatography or flash column chromatography, a better result was achieved by using MPLC (medium-pressure liquid chromatography). When 1000 mg of mono-ester mixture was applied to the MPLC operation, about 350 mg of pure (+)-**3** and 300 mg of pure (+)-**4** were obtained. With two pure diastereomers in hand, it was time to remove the auxiliary and retrieve the optically pure acids. When we tested hydrolysis under a mild basic condition, epimerization was observed by TLC monitoring. Without further testing more hydrolysis conditions, we shifted to the alternative method, the reduction and re-oxidation sequence, which is shown in Scheme 2. As far as the reduction was concerned, three reductants ($NaBH_4$, $LiBH_4$, and DIBAL) were compared. $NaBH_4$ and $LiBH_4$ gave a slow reaction with a low conversion, but DIBAL could completely convert the starting material to the product in two hours, from which two optically pure alcohols, (+)-**5** and (−)-**5**, were obtained in good yields.

Based on the reported $[\alpha]_D$ values of (*R*)-(+)-2-bromo-1-hexadecanol and (*S*)-(−)-2-bromo-1-hexadecanol,[7] we concluded that (+)-**5** was the *R*-isomer, while (−)-**5** was the *S*-isomer. Thus, the first diastereomeric ester (+)-**3** was formed from (*R*)-2-bromohexadecanoic acid, and the second diastereomeric ester (+)-**4** was formed from (*S*)-2-bromohexadecanoic acid. About 86% of the (*R*)-(+)-1,1′-bi-2-naphthol (*R*)-(+)-**2** used in the Steglich reaction was recovered from the DIBAL reduction. Optical rotation measurement showed the recovered binaphthol had the same optical purity as the commercial one, which indicated no loss of optical purity occurred to the chiral auxiliary and it could be re-used. The last step was to oxidize the alcohol to acid by Sharpless oxidation, which is a known experiment.[7] The reaction went smoothly to afford (*R*)-2-bromohexadecanoic acid or (*S*)-2-bromohexadecanoic acid in good yields.

The enantiomeric purity of the acids was assessed from the ^1H NMR spectrum using (1*R*,2*R*)-(+)-diphenylethane-1,2-diamine as a chiral solvating agent.[10,11] The diamine $CDCl_3$ solution was added, portion by portion, to the $CDCl_3$ solution of the acid. Then the ^1H NMR spectrum of the resultant mixture was recorded at once. For the (±)-2-bromohexadecanoic acid, in the presence of different equivalents of (1*R*,2*R*)-(+)-diphenylethane-1,2-diamine, the proton resonance of H-2 was resolved into two well-defined multiplets of equal intensity. With the adding of the diamine, although the chemical shifts of the multiplets and the distance between them varied, two well-resolved multiplets of 1:1 ratio were always observed. For the resolved (*R*)-acid, (*R*)-(+)-**1**, in the presence of different equivalents of (1*R*,2*R*)-(+)-diphenylethane-1,2-diamine, only one multiplet was observed, with no trace of the other multiplet. This clearly indicated the e.e. of the resolved (*R*)-(+)-acid was >95%. Similarly, in the presence of different equivalents of (1*R*,2*R*)-(+)-diphenylethane-1,2-diamine, (*S*)-(−)-**1** also constantly showed a single multiplet corresponding to the (*S*)-isomer, with no detectable resonance corresponding to the (*R*)-isomer. As in the previous case, the NMR integration suggested >95% enantiomeric excess for (*S*)-(−)-**1**.

3. Conclusion

In general, a long hydrocarbon chain on α-haloalkanoic acids makes resolution more difficult. The procedure disclosed herein allows for an efficient resolution of (*R*)- and (*S*)-2-bromohexadecanoic acids with high enantiomeric purity (e.e.>95%), starting from commercially available and inexpensive (±)-2-bromohexadecanoic acids. This protocol provided the desired two enantiomers with required optical purity, which are currently under STM study.[12]

4. Experimental

4.1. General

All materials were purchased from Aldrich. Solvents were distilled prior to use and dried by standard methods. Analytical and preparative TLC was run on precoated silica-gel plates (Analtech, 20×20 cm, 250 or 500 microns). The MPLC system consisted of an FMILAB Q-1SSY pump (Fluid Metering, Inc.) and an ULTRA Pack™ SI-40B column (Silica gel, 40 mm, 60 Å, size B 26×300 mm) (Yamazen Corporation). The eluting solvent was 20:1 hexanes:EtOAc. The flow rate was set to 6 milliliters per minute. When 1000 mg of mono-ester mixture was applied to the MPLC operation, about 350 mg of pure **3** and 300 mg of pure **4** were obtained. NMR data were collected on Bruker DMX 500 (500 MHz), 400 (400 MHz), and 300 (300 MHz) NMR spectrometers employing standard pulse sequences, operating at 500, 400, and 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR, respectively. Chemical shifts of ^{1}H and ^{13}C NMR signals were determined in ppm relative to the solvent signals of residual $CDCl_3$ at δ_H 7.24 ppm and δ_C 77.4 ppm, respectively. FAB mass spectra were recorded using a JEOL JMS-HX 110HF/HX 110HF tandem mass spectrometer. Infrared spectra were recorded on Perkin–Elmer Paragon 1000 FT-IR or Perkin–Elmer 1420 ratio recording infrared spectrophotometers. Optical rotations were measured on a Jasco DIP-1000 digital polarimeter.

4.2. Preparation of (R)-1,1′-bi-2-naphthyl (R)-2-bromohexadecanoate (+)-3 and (R)-1,1′-bi-2-naphthyl (S)-2-bromohexadecanoate (+)-4

To a flask which contained 118 mg (0.35 mmol) of racemic 2-bromohexadecanoic acid (±)-**1**, 100 mg (0.35 mmol) of (*R*)-(+)-1,1′-bi-2-naphthol ((*R*)-(+)-**2**), 80 mg (0.38 mmol) of DCC, and 47 mg (0.38 mmol) of DMAP, was added 8 ml of freshly distilled CH_2Cl_2. The reaction mixture was stirred at room temperature for one hour. The solid was filtered off and the organic solution was concentrated to dryness under reduced pressure and purified by column chromatography eluting with 20:1 hexanes:EtOAc to yield 194 mg (92.4%) of (+)-**3** and (+)-**4**.

4.2.1. (R)-1,1′-Bi-2-naphthyl (R)-2-bromohexadecanoate (+)-3

$[\alpha]_D^{19} = +75.8$ (*c* 1.00, $CHCl_3$). IR (film): 3600–3100, 3020, 2880, 2820, 1730, 1602, 1580 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, $J=8.9$ Hz, 1H), 7.98 (d, $J=8.2$ Hz, 1H), 7.88 (d, $J=8.9$ Hz, 1H), 7.83 (d, $J=8.1$ Hz, 1H), 7.53 (t, $J=7.0$ Hz, 1H), 7.44 (d, $J=8.9$ Hz, 1H), 7.37–7.25 (m, 7H), 7.05 (d, $J=8.4$ Hz, 1H), 5.10 (bs, 1H), 3.97 (t, $J=7.4$ Hz, 1H), 1.53 (m, 2H), 1.29 (bs, 16H), 1.19 (m, 2H), 1.10 (m, 2H), 0.99 (m, 3H), 0.90 (t, $J=7.0$ Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 152.2, 148.0, 133.9, 133.8, 132.8, 131.5, 131.0, 129.5, 128.8, 128.4, 128.1, 127.3,

127.0, 126.2, 124.9, 124.0, 123.5, 121.4, 118.6, 114.0, 45.3, 34.7, 32.4, 30.2, 30.1, 29.9, 29.8, 29.5, 29.1, 27.1, 23.1, 14.6. HRFABMS calcd for $C_{36}H_{43}BrO_3$: 602.2396; found: 602.2392.

*4.2.2. (*R*)-1,1′-Bi-2-naphthyl (*S*)-2-bromohexadecanoate (+)-**4***

$[\alpha]_D^{18}=+32.6$ (*c* 1.00, $CHCl_3$). IR (film): 3600–3100, 3022, 2885, 2821, 1732, 1602, 1580 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, $J=8.9$ Hz, 1H), 7.98 (d, $J=8.2$ Hz, 1H), 7.88 (d, $J=8.9$ Hz, 1H), 7.82 (d, $J=8.0$ Hz, 1H), 7.53 (t, $J=7.0$ Hz, 1H), 7.44 (d, $J=8.9$ Hz, 1H), 7.37–7.24 (m, 7H), 7.06 (d, $J=8.3$ Hz, 1H), 5.06 (bs, 1H), 3.98 (t, $J=7.5$ Hz, 1H), 1.40 (m, 2H), 1.29 (bs, 16H), 1.17 (m, 2H), 1.02 (m, 3H), 0.89 (t, $J=7.1$ Hz, 5H), 0.71 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 152.1, 147.9, 133.9, 133.8, 132.8, 131.4, 130.9, 129.5, 128.8, 128.4, 128.1, 127.3, 127.0, 126.1, 124.9, 124.0, 123.5, 121.4, 118.6, 113.9, 45.5, 34.6, 32.4, 30.1, 30.04, 29.9, 29.8, 29.4, 29.1, 27.1, 23.1, 14.6. HRFABMS calcd for $C_{36}H_{43}BrO_3$: 602.2396; found: 602.2410.

*4.3. (*R*)-(+)-2-Bromo-1-hexadecanol (*R*)-(+)-**5***

To a dried flask which contained 59.6 mg (0.1 mmol) of (+)-**3** was added 3 ml of freshly distilled CH_2Cl_2. The solution was cooled to −78°C. Then 0.25 ml of 1 M DIBAL hexanes solution was slowly added. The reaction mixture was stirred at −78°C and monitored by TLC until starting material was completely consumed. 0.5 ml of MeOH was added to the reaction mixture, then 5 ml of CH_2Cl_2 was added and the mixture was brought to room temperature. 1 ml of water was added and the mixture was stirred for 30 minutes. After filtration through Celite, the mixture was concentrated under reduced pressure and separated by flash chromatography eluting with 5% EtOAc in hexanes to yield 24.6 mg (77.6%) of (*R*)-(+)-**5** (with recovered 24.1 mg (86%) of binaphthol (*R*)-(+)-**2**). $[\alpha]_D^{22}=+20.4$ (*c* 1.00, $CHCl_3$). IR (film): 3600–3100, 2920, 2851, 1457, 1376, 1071, 1029, 720, 634, 531 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.12 (m, 1H), 3.76 (m, 2H), 1.97 (bs, 1H), 1.82 (m, 2H), 1.50 (m, 1H), 1.40 (m, 1H), 1.23 (bs, 22H), 0.86 (t, $J=7.0$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 67.7, 60.6, 35.3, 32.3, 30.1, 29.9, 29.8, 29.76, 29.4, 27.8, 23.1, 14.5. HRFABMS calcd for $C_{16}H_{33}BrO$: 321.1618; found: 321.1608.

*4.4. (*S*)-(−)-2-Bromo-1-hexadecanol (*S*)-(−)-**5***

Following the same procedure, from 420 mg of ester (+)-**4**, 193 mg (86%) of alcohol (*S*)-(−)-**5** was obtained. $[\alpha]_D^{20}=-19.1$ (*c* 1.00, $CHCl_3$). IR (film): 3600–3100, 2920, 2851, 1457, 1376, 1071, 1029, 720, 634, 531 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.12 (m, 1H), 3.76 (m, 2H), 1.99 (bs, 1H), 1.82 (m, 2H), 1.50 (m, 1H), 1.40 (m, 1H), 1.24 (bs, 22H), 0.86 (t, $J=7.0$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 67.7, 60.6, 35.3, 32.3, 30.1, 29.9, 29.8, 29.75, 29.4, 27.8, 23.1, 14.5. HRFABMS calcd for $C_{16}H_{33}BrO$: 321.1618; found: 321.1629.

*4.5. (*R*)-(+)-2-Bromohexadecanoic acid (*R*)-(+)-**1***

A solution of 70 mg (0.22 mmol) of alcohol (*R*)-(+)-**5** in 1.4 ml of CCl_4, 1.4 ml of CH_3CN was treated with 2.1 ml of H_2O, 190 mg (0.89 mmol) of $NaIO_4$ and 17 mg (0.082 mmol) of $RuCl_3{\cdot}3H_2O$. The resulting heterogeneous mixture was vigorously stirred at room temperature. After 3 and a half hours, the reaction mixture was diluted with 14 ml CH_3CN, the remaining solids were removed through Celite, and the solution was evaporated to dryness under reduced pressure, then was added 40 ml CH_2Cl_2 and washed with water. The organic layer was dried

over Na_2SO_4, filtered and evaporated to give crude acid, which was purified by boiling in hexanes in the presence of charcoal. After filtration and evaporation, the solid was left overnight and then dissolved in MeCN. Filtration through Celite and evaporation afforded (*R*)-(+)-**1** as a white solid (58 mg, 80%). $[\alpha]_D^{22} = +21.2$ (*c* 1.00, $CHCl_3$). IR ($CHCl_3$ solution): 3300–2500, 2981, 2890, 2820, 1699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.22 (t, $J = 7.4$ Hz, 1H), 2.01 (m, 2H), 1.46 (m, 1H), 1.38 (m, 1H), 1.24 (bs, 22H), 0.86 (t, $J = 6.9$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.9, 45.7, 35.1, 32.3, 30.0, 29.9, 29.8, 29.7, 29.2, 27.6, 23.1, 14.5. HRFABMS calcd for $C_{16}H_{31}BrO_2$: 335.1586; found: 335.1597.

*4.6. (S)-(−)-2-Bromohexadecanoic acid (S)-(−)-**1***

Following the same procedure, from 129 mg of (*S*)-(−)-**5**, 110 mg (82%) of (*S*)-(−)-**1** was obtained. $[\alpha]_D^{22} = -21.2$ (*c* 1.00, $CHCl_3$). IR ($CHCl_3$ solution): 3300–2500, 2981, 2890, 2820, 1699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.22 (t, $J = 7.4$ Hz, 1H), 2.01 (m, 2H), 1.46 (m, 1H), 1.38 (m, 1H), 1.24 (bs, 22H), 0.86 (t, $J = 6.9$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1, 45.8, 35.1, 32.3, 30.1, 29.9, 29.8, 29.7, 29.2, 27.6, 23.1, 14.5. HRFABMS calcd for $C_{16}H_{31}BrO_2$: 335.1586; found: 335.1588.

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